Thrombotic complications in oncogynecological pathologies

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ABSTRACT

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) are well-recognized complications of gynecological malignancy and represent a leading cause of morbidity and mortality in these patients. It is known that pulmonary embolism (PE) is the cause of death in up to 15% of patients hospitalized due to a tumor. A significant proportion of cancer patients with fatal PE have a tumor of limited size or a metastatic process of minimal prevalence, i.e., we are talking about patients with a high chance of recovery or a long life. According to various researchers, from 4 to 20% of all cancer patients experience clinical manifestations of venous thromboembolism (venous thrombosis and/or pulmonary embolism). At the same time, the absolute frequency of this complication in cancer varies widely: it can be either standard for a healthy population (early breast cancer - less than 1%), or extremely high, amounting to 11,7% in cervical cancer.

Keywords: Venous thromboembolism, oncogynecological cancer, morbidity

Epidemiology. There is huge disparity in the reported incidence of VTE in patients with gynecological malignancy, ranging between 3% and 25% across their life-span. It is likely that a variety of variables affect the conveyed incidence, which notably include the type of malignancy, the stage, and whether or not the patient has commenced treatment [2,3]. However, the range in incidence will also be influenced by the method of diagnosis. One large American study including 853 cancer patients (among which were 289 cervical, 195 ovarian, 255 uterine, and 36 vulvar) found the overall incidence of DVT to be 4,2% [4]. A further nationwide study in Taiwan of 1013 patients with cervical cancer found the incidence of VTE to be 3.3% [5]. However, incidence figures for cervical cancer had been quoted as high as 11,7% [1]. A small Japanese study reported the pretreatment incidence of DVT and DVT + PE in endometrial cancer as 9.9% and 4.7%, respectively [6]. The incidence quoted for ovarian cancer in a study of more than 13,000 women in the California cancer registry was 5.2% [7]. Another study that conducted for postoperative risk of VTE in patients with vulvar carcinoma indicates that 11 (0,8 %) (out of 1414) patients developed VTE [2]. Furthermore, one retrospective study including 104 368 gynecologic operations (11

427 performed for malignancy) reported that 202 (1,8 %) patients experienced a VTE, while Compared with all gynecologic cancer surgeries, ovarian cancer patients were 1,5 times more likely to have a VTE [10]. The broad range is likely due to heterogeneity of population groups and study designs.

Risk factors. 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]. Many surgical and anatomical factors alter the three factors described by Virchow (encompassing hypercoagulability, hemostasis, and endothelial injury), thereby promoting the development of DVT. Despite incongruence in specific numerical figures, it is abundantly clear that malignancy itself is an independent risk factor for development of VTE [4, 11]. Furthermore, 10,5% of patients presenting with an idiopathic VTE will have a diagnosis of cancer within 5 to10 years, with the majority diagnosed in the first year [12]. 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. Within the gynecological cancer cohort patients older than 60 years having a 4-fold increased risk compared with their younger counterparts (10,4% vs 2,6%). Specific tumor factors including type, size, and stage were also implicated in the risk profile. Considering cervical cancer, tumors of greater than 50 mm increased the risk of VTE by almost 9 times (10,2%>50mm vs 1,2%<50mm). It was concluded that the increased risk is likely due to the large pelvic tumor size impairing venous return, causing hemostasis and therefore a predisposition to clotting [3]. Moreover, it is suspected that damage to the pelvic venous plexus during radiotherapy may increase the risk of VTE. A prospective study of 411 gynecology patients identified previous pelvic radiation therapy as a statistically significant risk factor in the development of DVT [17]. Surgery itself is a risk factor for VTE, as it 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. Additionally, embryologically, pelvic lymphatics arise from the pelvic veins. Thereby, there can be venous trauma, developing DVT during the dissection of lymph nodes. In one of the largest studies looking at 397 patients who underwent radical abdominal hysterectomy for cancer, 2.7% developed a VTE [13]. By comparison, the incidence of VTE after open hysterectomy for benign conditions was only 0,6% (81/12,733patients) [18]. Postoperative PE remains the primary cause of mortality after gynecological cancer surgery [14]. Although chemotherapy increases survival in patients with high-risk tumors, it also carries a significant VTE risk [15]. A large American study looking at incidence of VTE among cancer patients undergoing chemotherapy found that in the 12 months after initiation of treatment, 12,6% overall developed a VTE (compared with just 1.4% in the control group) [16]. Moreover, anesthetic drugs may cause venous distension, aggravating the sluggish blood flow in pelvic vessels, thus increasing the risk of VTE.

Pathogenesis. The pathogenesis of venous thromboembolism (VTE) after oncogynecological cancer surgery is multifactorial, involving a complex interplay of cancer-related, surgery-related, and patient-specific factors. It is well documented in the literature that cancer growth is associated with the development of a procoagulant state [19]. Histopathological analysis of tumor specimens has revealed the presence of fibrin strands and platelet aggregates surrounding the tumors, indicating that aggressive tumors exploit the coagulation cascade to facilitate their rapid growth [20]. Broadly speaking, there are three key mechanisms behind this phenomenon. Firstly, malignant cells enable significant procoagulant, fibrinolytic and proaggregating activity through the significant release of tissue factors [21]. Secondly, they release proinflammatory and proangiogenic cytokines, including tumor necrosis factor and interleukin - 1 [21]. Third, they have high expression of

adhesion molecules, such as integrins, cadherins, and selectins interacting directly with host vascular and blood cells [22]. The latter two lead to the activation of the host's procoagulant and proadhesive cells, which simultaneously downregulate the anticoagulant response [21]. The main cells involved in this process are endothelial cells, platelets and leukocytes. The result of the combined activation of these signaling pathways is increased thrombin and fibrin production and thus a prothrombotic state [21]. Moreover, large pelvic tumors can compress pelvic veins obstructing venous return and leading to hemostasis and subsequent thrombus formation. Furthermore, larger cervical tumors are more prone to invading the parametria and pelvic wall, which may result in endothelial cell damage [23]. Beyond the malignancy itself, certain therapeutic interventions can also contribute to thrombus formation. For instance, chemotherapy is known to induce endothelial damage, with agents such as bleomycin causing an immediate disruption of endothelial cell integrity. Additionally, reduced mobility following surgery diminishes the pump action of the gastrocnemius muscle, leading to increased venous pooling and stasis [22]. Furthermore, 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 [23].

Clinical presentation and diagnosis. When studying the problem, several articles about oncogynecological pathology were analyzed [23, 42]. As deep vein thrombosis and pulmonary embolism are frequent and potentially severe complications associated with gynecological malignancies, it is essential for clinicians to possess a thorough understanding of their typical presenting symptoms. One study involving 893 patients with malignancy (including gynecological, breast, and anal cancers) found that leg edema, erythema, and warmth were the symptoms most likely to indicate a DVT [24]. A subsequent study determined that 50% to 80% of patients presenting with classic symptoms, such as erythema and swelling, do not have a DVT, as these symptoms lack high specificity [25]. Regarding pulmonary embolism, the traditional symptoms of hemoptysis and pleuritic chest pain appear to be uncommon. In a study involving 72 patients, the 8 individuals diagnosed with PE through pulmonary scintigraphy were all asymptomatic [26]. Consequently, clinicians should maintain a low threshold for further investigation when VTE is suspected, even in the absence of classic symptoms. In some patients, a DVT or PE can be the first presentation of an occult malignancy. Often, these cases can be severe with bilateral DVT, recurrent DVT, or iliofemoral DVT. A review of studies revealed a 2- to 5-fold increase in the risk of occult cancer among patients with idiopathic venous thromboembolism, with this risk being particularly pronounced for malignancies of specific internal organs, such as the ovary, brain, and pancreas [27]. Occasionally, there can be more unusual manifestations of the hypercoagulable state associated with malignancy. One case report outlined microtumor embolus leading to severe cor pulmonale [28]. Similarly, vascular paraneoplastic syndromes are uncommon but may serve as the initial indication of an underlying gynecological malignancy [27]. Patients with gynecological malignancies undergoing surgery must have a proper assessment of the postoperative risk of VTE. Compression vein ultrasonography with color Doppler flow or duplex ultrasonography is the most frequently used test in the diagnosis of DVT [29]. The sensitivity and specificity, while varying depending on the operator, have been documented to range between 82% and 96%, and 97% and 100%, respectively [30]. Other imaging modalities such as computed tomography (CT) and magnetic resonance venography with relatively high sensitivity and specificity are also increasingly being used particularly to assess for iliofemoral DVT, although duplex ultrasonography should remain the first-line investigation. Catheter

venography, formerly considered the gold standard diagnostic method, should now be reserved for cases where interventional treatments, such as thrombolysis, are planned due to its invasive nature. CT pulmonary angiography remains the criterion standard in the diagnosis of PE [31]. However, CT venography has been examined in combination with CT pulmonary angiography to assess the diagnostic impact of examining the pelvic veins simultaneously during the scan. The results indicate a slight increase in the percentage of patients diagnosed; however, the risk-benefit ratio associated with this marginal improvement remains a subject of debate [32].

D-dimer (DD) has been identified the strongest prognostic biomarker for VTE in patients with cancer. D-dimer is a fibrin degradation product present after a blood clot has been degraded by fibrinolysis and levels are frequently elevated in cancer patients even in the absence of VTE. Several studies have reported that levels of plasma DD before treatment in most ovarian cancer patients are increased and related to advanced disease, suggesting DD as a useful tumor marker or prognostic factor of ovarian cancer [33]. Although high levels of DD are generally thought to be with the presence of DVT, one study reported that preoperatively increased DD levels in ovarian cancer are not significantly associated with risk of subsequent DVT in the postoperative period and during first-line chemotherapy [34]. In that study, patients were administered either low-molecular-weight heparin or unfractionated heparin as perioperative anticoagulant therapy, initiated 2 hours prior to surgery and continued until postoperative day 7. However, the study did not investigate the relationship between elevated D-dimer levels and the presence of silent venous thromboembolism (VTE) before surgery. Another extensive research has been conducted to explore the role of D-dimers in predicting venous thromboembolism (VTE), current findings restrict their utility to the exclusion of VTE in patients with D-dimer levels below 1,5 kg/mL, which demonstrates a negative predictive value exceeding 95% [35]. Its sensitivity and specificity for isolated DVT are 84% and 50%, respectively, thus limiting its use as a diagnostic tool [35].

Prevention. Venous thromboembolism, even in high-risk cancer patients, is considered one of the most common causes of preventable hospital death. Prophylactic methods have significantly reduced the incidence of VTE after major surgery. Several methods are available for VTE prophylaxis following surgery for gynecological malignancies. These methods should be cost-effective, practical, free of significant side effects, acceptable to both patients and healthcare staff, and broadly applicable to the majority of patients. Venous thromboembolism prophylaxis methods can generally be categorized into mechanical and pharmacological approaches. Firstly, prolonged surgical duration and postoperative immobilization contribute to venous stasis, particularly in the calf muscle veins. To mitigate stasis, early ambulation, elevation of the lower extremities, and adequate hydration are strongly recommended. Well-fitted stockings have shown a modest benefit in preventing VTE. It is simple to use, low cost and without any significant side effects and is often used in the routine postoperative periods [36]. Additionally, intermittent pneumatic compression (IPC) devices reduce stasis by intermittently compressing the calf with a sleeve inflated to 50 mmHg by a pneumatic pump. This enhances venous flow, leading to a pulsatile emptying of the calf veins. It also promotes endogenous fibrinolysis, facilitating the early dissolution of thrombi before they become clinically significant.[37] When used intraoperatively and in the postoperative period, IPC devices have comparable effectiveness to low molecular weight heparin (LMWH) in preventing DVT. Intermittent pneumatic leg compression is more cost-effective than pharmacological methods and carries no significant side effects or risks. Additionally, it serves as the primary prophylactic measure immediately after surgery, when the use of anticoagulants is not feasible. 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. VTE prophylaxis is advised for all hospitalized medical or surgical patients with cancer, as limited ambulation following admission increases the risk of VTE. Low-dose heparin has been shown to prevent VTE and its associated mortality in both major benign and oncologic surgeries [38]. The available anticoagulants for patients undergoing gynecologic oncologic surgery include unfractionated heparin, low-molecule heparin, fondaparinux, and apixaban. Low molecular weight heparin (LMWH) 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. However, its cost exceeds that of heparin. It also has a longer half-life compared to heparin, enabling once-daily dosing.[39] Unfractionated heparin (UFH) is the most extensively studied pharmacologic method for preventing DVT. When administered at a dose of 5,000 units 2 hours preoperatively and every 8 hours postoperatively, it has demonstrated significant effectiveness in preventing DVT in patients with gynecological malignancies. However, its use has been limited by a slightly increased risk of bleeding and heparin-induced thrombocytopenia [40]. Fondaparinux is an indirect inhibitor of activated factor Xa, which potentiates antithrombin. 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%), it was found to be as efficacious as LMWH in the prevention of postoperative VTE [41].

Conclusions: DVT is the most common postoperative complication in patients with oncogynecological pathology. Anatomical confinement, closed dependent 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. Understanding these mechanisms highlights the importance of prophylactic measures, such as anticoagulation, early ambulation, and mechanical compression devices, to minimize the risk of VTE in this high-risk population.

References:

1. Jacobson G, Lammli J, Zamba G, et al. Thromboembolic events in patients with cervical carcinoma: incidence and effect on survival. Gynecol Oncol. 2009;113:240Y244.
2. Эргашев М. М., Абдурахимов О. Н., Турсунова Н. И. Распространенность и проблемы диагностики юношеской ангиофибромы //European research. – 2017. – №. 8 (31). – С. 56-58.
3. Satoh T, Matsumoto K, Tanaka YO, et al. Incidence of venous thromboembolism before treatment in cervical cancer and the impact of management on venous thromboembolism after commencement of treatment. Thromb Res. 2013;131: e127Ye132.
4. Santoso JT, Evans L, Lambrecht L, et al. Deep venous thrombosis in gynecological oncology: incidence and clinical symptoms study. Eur J Obstet Gynecol Reprod Biol. 2009;144:173Y176.
5. Tsai SJ, Ruan YX, Lee CC, et al. The incidence of venous thromboembolism in cervical cancer: a nationwide population-based study. BMC Res Notes. 2012;5:316.
6. Satoh T, Matsumoto K, Uno K, et al. Silent venous thromboembolism before treatment in endometrial cancer and the risk factors. Br J Cancer. 2008;99:1034Y1039.
7. Rodriguez AO, Wun T, Chew H, et al. Venous thromboembolism in ovarian cancer. Gynecol Oncol. 2007;105:784Y790.
8. Ray MD. Bowled out phenomenon- after cytoreductive surgery/hyperthermic intraperitoneal chemotherapy: Review of literature with our experience in high volume tertiary care centre in India. Multidisciplinary Approach to Surgical Oncology Patients. 1st edn. Springer; 2019.
9. Trousseau A. Phlegmasia alba dolens. In: Clinique Medicale de L'Hotel-Dieu Paris. London: New Syndenham Society; 1865:94-96.
10. Ashley Graul, Nawar Latif, Xiaochen Zhang et al. Incidence of Venous Thromboembolism by Type of Gynecologic Malignancy and Surgical Modality in the National Surgical Quality Improvement Program. Int J Gynecol Cancer; 2009.(3):581-587/

11. Wharin C, Tagalakis V. Management of venous thromboembolism in cancer patients and the role of the neworal anticoagulants. Blood Rev. 2014;28:1Y8.
12. PrandoniP, Lensing AW,Bu ¨ller HR, etal. Deep-veinthrombosis and the incidence of subsequent symptomatic cancer. N Engl J Med. 1992;327:1128Y1133.
13. Sivanesaratnam V, Sen DK, Jayalakshmi P, et al. Radical hysterectomy and pelvic lymphadenectomy for early invasive cancer of the cervixV14-yearexperience. Int J Gynecol Cancer. 1993;3:231Y238.
14. Clarke-Pearson DL, Jelovsek FR, Creasman WT. Thromboembolism complicating surgery for cervical and uterine malignancy: incidence, risk factors, and prophylaxis. Obstet Gynecol. 1983;61:87Y94.
15. 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;160:809Y815.
16. Khorana AA, Dalal M, Lin J, et al. Incidence and predictors of venous thromboembolism (VTE) among ambulatory high-risk cancer patients undergoing chemotherapy in the United States. Cancer. 2013;119:648Y655.
17. Clarke-Pearson DL, DeLong ER, Synan IS, 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;69:146Y150.
18. Barber EL, Neubauer NL, Gossett DR. Risk of venous thromboembolism in abdominal versus minimally invasive hysterectomy for benign conditions. Am J Obstet Gynecol. 2015;212:609.e1Ye609.e7
19. Falanga A, Donati MB. Pathogenesis of thrombosis in patients with malignancy. Int J Hematol. 2001;73:137Y144.
20. Isroilovna T. N. et al. Klippel-Trenaunay syndrome in combination with ovarian cancer //British View. – 2023. – T. 8. – №. 4.
21. Piccioli A, Falanga A, Baccaglini U, et al. Cancer and venous thromboembolism. Semin Thromb Hemost. 2006;32:694Y699
22. Rickles FR, Falanga A. Molecular basis for the relationship between thrombosis and cancer. Thromb Res. 2001;102: V215YV224.
23. Isroilovna T. N., Ergashevna A. N. Epidemiological aspects of the incidence of endometrial cancer in the city of Tashkent //Asian Journal of Multidimensional Research (AJMR). – 2018. – T. 7. – №. 10. – C. 135-139.
24. Santoso JT, Evans L, Lambrecht L, et al. Deep venous thrombosis in gynecological oncology: incidence and clinical symptoms study. Eur J Obstet Gynecol Reprod Biol. 2009;144:173Y176.
25. Dainty L, Maxwell GL, Clarke-Pearson DL, et al. Cost effectiveness of combination thromboembolism prophylaxis in gynecologic oncology surgery. Gynecol Oncol. 2004;93:
26. Satoh T, Oki A, Uno K, et al. High incidence of silent venous thromboembolism before treatment in ovarian cancer. Br J Cancer. 2007;97:1053Y1057.
27. Rickles FR, Falanga A. Molecular basis for the relationship between thrombosis and cancer. Thromb Res. 2001;102: V215YV224.
28. Dhelaria RK, Acevedo C, Fadaili A, et al. Microtumor embolization leading to cor pulmonale: an extremely rare complication of ovarian cancer. South Med J. 2010;103:720.
29. Davis JD. Prevention, diagnosis, and treatment of venous thromboembolic complications of gynecologic surgery. Am J Obstet Gynecol. 2001;184:759Y775.
30. Lensing AW, Prandoni P, Brandjes D, et al. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. N Engl J Med. 1989;320:342Y345.
31. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition n). Chest. 2008;133:381SY453S.
32. Nazarolu H, Ozmen CA, Akay HO, et al. 64-MDCT pulmonary angiography and CT venography in the diagnosis of thromboembolic disease. AJR Am J Roentgenol. 2009;192:654Y661.
33. Mirshahi SS, Pujade-Lauraine E, Soria C, Mirshahi M, Fretault J, Bernadou A, Soria J(1992)-dimer and CA125 level in patients with ovarian cancer during antineoplastic treatment.Cancer69:2289–2292
34. von Tempelhoff GF, Dietrich M, Niemann F, Schneider D, Hommel G, Heilmann L (1997)

Blood coagulation and thrombosis in patients with ovarian cancer. Thromb Haemost 77: 456–461
35. Sartori M, Cosmi B, Legnani C, et al. The Wells rule and D-dimer for the diagnosis of isolated distal deep vein thrombosis. J Thromb Haemost. 2012;10:2264Y2269.
36. Barber EL, Clarke-Pearson DL. The limited utility of currently available venous thromboembolism risk assessment tools in gynecological oncology patients. Am J Obstet Gynecol. 2016;215(4):445-e1.
37. Stroud W, Whitworth JM, Miklic M, Schneider KE, Finan MA, Scalici J, et al. Validation of a venous thromboembolism risk assessment model in gynecologic oncology. Gynecol Oncol. 2014;134:160-3.
38. Salzman EW, Ploetz J, Bettmann M, Skillman J, Klein L. Intraoperative external pneumatic calf compression to afford long-term prophylaxis against deep vein thrombosis in urological patients. Surgery. 1980;87(3):239-42.
39. Maxwell GL, Synan I, Dodge R, Carroll B, Clarke Pearson DL. Pneumatic compression versus low molecular weight heparin in gynecologic oncology surgery: a randomised trial. Obstet Gynecol. 2001;98:989-95.
40. Baykal C, Al A, Demirtaş E, Ayhan A. Comparison of enoxaparin and standard heparin in gynaecologic oncologic surgery: a randomised prospective double blind clinical study. Eur J Gynecol Oncol. 2001;22(2):127-30.
41. Tapson VF, Hull RD. Management of venous thromboembolic disease. The impact of low molecular-weight heparin. Clin Chest Med.1995;16(2):281-94.
42. Tursunova Nodira Isroilovna, Atakhanova Nigora Ergashevna The significance of preoperative radiation therapy in the treatment of uterine body cancer, depending on p53 and bcl-2 // European science review. 2018. №7-8.