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The effect of surgical interventions for gynaecological malignancies on red blood cell indices and hemostaseologic parameters

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Summary

The goal of this study was to monitor changes of common hemostaseologic parameters, serum protein concentration red blood cell (RBC) indices and erythrocyte sedimentation rate (ESR) in women with malignant and non-malignant gynecologic disease preoperatively and in the early postoperative period (five days).One hundred fifty-two women with a primary diagnosis of gynaecological malignancy and a matched group of women undergoing surgery for non-malignant disorders were enrolled in the study. Patients with severe comorbity or venous thrombosis events in the recent history (< six months) were excluded. Preoperatively, coagulation markers including fibrinogen- and D-Dimer-levels were statistically significantly higher, while pTTT was prolonged in all cancer patients compared to the benign tumor patients. Mean albumin/globulin ratio (A/G-R) was lower in each of the cancer types being lowest in ovarian cancer patients while RBC indices (MCH, MCV, and MCHC) were comparable with those of the benign disease group. However, ESR was significantly higher in all types of cancer compared to the controls. Postoperatively, in the cancer groups, mean values of coagulation markers increased and remained significantly higher as compared to the preoperative values until day 5. A/G-R slightly but statistically significantly dropped postoperatively, being lowest in patients with ovarian cancer. While in the cancer patients, ESR statistically significantly increased postoperatively and remained high until day 5 it remained unchanged after surgery for benign disease. The preoperative use of common routine laboratory markers may allow differentiation of dignity in patients with benign and malign gynecologic disease. Moreover, the divergence of the results postoperatively correlate with the extent of the intervention and the tumor load being most remarkable after ovarian cancer surgery.

Key words: Gynaecological malignancies; Surgery; Coagulation; RBC indices; ESR.

Introduction

The association between thromboembolic events and cancer dates back to Armand Trousseau almost 150 years ago, who observed the common appearance of venous thromboembolism (VTE) with malignancy in gastric and pancreatic cancer [1]. Subsequently, a tremendous number of literature based on different sources including cancer registries, retrospective cohorts, and prospective population-based observational studies confirmed an increasing incidence of cancer in patients with VTE (6.5-16.5%) compared to others without the referred disease (1.8-7.1%) [1].

Cancer disease bears a four to seven times increased risk of VTE compared to those without the malignancy disease [2]. According to previously reports the estimated annual incidence of thromboembolism in the cancer population is 0.5% and it is the second leading cause of death in this patients' population [3].

Cancer associated VTE has a multifactorial pathophysiology, whereas all aspects of the triad of Virchow are commonly imbalanced in cancer patients, among which the most common thrombosis predisposing factors includes a hypercoagulable state based on inflammatory actions, coagulation factor increase e.g. FVIII, Tissue Factor expression, and acquired resistance to activated protein C. Moreover, endothelial dysfunction linked to the prothrombotic impact of tumour cell cytokines, venous stasis subsequent to immobilization during hospitalization, venous compression due to tumor expansion or adenopathies, and reduced blow flow induced by impaired blood rheological properties e.g. hyper viscosity are common co-risk factors of thrombosis in the cancer patients [4, 5].

Tissue factor (TF) is the physiologic initiator of coagulation and an important biomarker for cancer associated VTE [6]. Cancer cells activate the clotting system through thrombin, stimulate mononuclear cells, release inflammatory cytokines, and enhance platelet aggregation [7]. Cancer procoagulant is a cysteine proteinase specific to cancer cells that directly activates factor X, independently of factor VII [4, 5]. Tumor vasculature is characterized by re-

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duced functionality of endothelium in the blood vessels that leads to blood rheologic changes, initiates coagulation activation, inflammatory processes, proteolysis, and paraproteinaemia [6, 8].

The aim of this study was to compare the pre- and postoperative results of common laboratory parameters in gynaecological cancer patients with those in women undergoing surgery for benign non-inflammatory indications, and to compare results within different gynecologic tumor entities.

Materials and Methods

Patients with confirmed histologically type of gynecological cancer (breast, endometrial, ovarian, and vulvar carcinoma) were enrolled in the study. In cases with presence of two or more histologic subtypes, the predominant subtype was used, which was defined as the present type more than 90% of the total tumor. The study protocol was approved by the Ethics Committee of Alexandroupolis University Hospital. Written informed consent was obtained from all participants. This study was also conducted in accordance with the Declaration of Helsinki. Data assessment included: cancer origin, FIGO stage, age, parity, menopausal status, body mass index (BMI), histological subtype, operative records, operative time, estimated blood loss, smoking status, comorbid conditions like: hypertension, severe pulmonary, cardiac, renal, hepato-pancreatic, peripheral vascular, or autoimmune disease, stroke, and diabetes. Patients with a history of prior deep venous thrombosis (< six months), or being on anticoagulant drugs, and those with a history of malignant disease were excluded. Tumor staging was defined according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system, and based on the final histological findings and objective evaluations reports. None of the participants had received blood transfusions within ten days before surgical intervention.

Routine preoperative testing included blood analysis, electrocardiogram, chest radiography, and ultrasound of the genitals and breast in all participants with gynecological cancer and benign disease as well. Indications for surgery in participants without cancer included removal of breast fibroma, vulvar fibroma, uterine myoma, ovary fibroma/cysts.

All pelvic oncological patients underwent primary surgery which included: hysterectomy, bilateral salpingo-oophorectomy, high resection of the infundibulo-pelvic ligaments, omentectomy, appendectomy, and pelvic sampling lymphadenectomy. Surgery for benign conditions included lumpectomy, hysterectomy, cyst removal of the ovary/adenectomy, and tumor excision of the vulvar,

Blood loss was measured at the completion of surgery by subtracting flushing fluids from that in all draining reservoirs. Times of surgery were defined as cut-seam times which included waiting times for intraoperative histological evaluation and histological clarification of tumor margins and lymph node involvement. Patients with histological confirmed breast cancer underwent either lumpectomy (removal of the tumor with a small area of "security" around it) or modified radical mastectomy with dissection of level I and II axillary lymph nodes in case of a positive sentinel lymph node. The corresponding patients with benign breast tumors underwent a simple tylectomy. Blood sampling and laboratory assessments in both groups took place the day before primary operation and again in the morning of the first, third, and fifth postoperative days. The following routine was performed: hemoglobin (Hg): 11.5-15.5 g/dl), hematocrit (HCT): 35.0-45.0%, platelet count (Plt): 150-400 k/μl, (fibrinogen: 220-490 mg/dl), mean corpuscular volume (MCV): 76.0-96.0 fl, mean corpuscular hemoglobin (MCH): 27.0-34.0, mean corpuscular hemoglobin (MCHC) concentration: 25.0-32.0 g/dl, ESR: 10-20 mm/h, activated partial thromboplastin (aPTT): 25.00-37.00 sec., protein: 5.5-8 g/dl, albumin: 3.5-5.5 g/dl, albumin/globulin (A/Gl-R): 1.1-2 g/dl, and D-Dimer (Dim): 64-495 ng/ml.

SPSS 20.0 was used for data processing. All tests were two-sided, with significance set at $p < 0.05$. The measurement data are presented as means ± standard deviation, and inter-group comparisons were performed with the paired-*t*-test while differences between longitudinal results were assessed using Friedman test. Enumerated data are presented as cases (constituent ratio), and inter-group comparisons were performed with the Pearson chi-squared test or Fisher exact test.

Results

A total of 152 eligible women with a primary diagnosis of gynecological cancer (group A) and similar number of participants with benign diseases (group B) from the Department of Gynecology and Obstetrics University Hospital Alexandroupolis were identified during the period from April 2010 to June 2015**.** Demographic data of both groups including age, menopausal status, nicotine abuse, weight, and BMI are presented in Table 1. There was no statistical significant difference between these two groups for none of the baseline characteristics. Table 2 summarizes histological findings, cancer stages according to FIGO, and TNM Classifications, as well as histological subtypes, median values of operation's time, and bleeding volume loss during surgery.

The most frequent type of cancer was breast cancer (43%; 65/152), followed by endometrial- (32%; 49/152) and ovarian cancer (23%; 35/152). Patients with histologically confirmed carcinoma of the vulva were eligible to participate in the study but were few in number (2%; 3/152). In patients with pelvic malignant tumors the medium cut-seam time was 276 ± 35 minutes, the medium bleeding volume loss was 255 ± 25 ml, while in the control group with benign disease the medium cut-seam time was 124 ± 15 minutes, and medium bleeding loss was 95 ± 10 ml, respectively. Results in the breast cancer patients were 106 ± 19 minutes for cut-seam time and 75 ± 15 ml for bleeding loss, while surgery for benign disease went along with a mean cut-seam time of 44 ± 10 minutes, and bleeding loss of 25 ± 10 ml, respectively ($p < 0.01$). In Table 3 the results of laboratory findings preoperatively and in the early postoperative period at days 1, 3, and 5 are summarized.

In the malignancy group the preoperative concentrations of Hg and HCT were highest in participants with endometrial cancer and lowest in ovarian cancer patients. The fibrinogen concentration, ESR, MCV, and MCHC were highest in ovarian cancer patients, while MCH and A/G-R

Table 1. — *Characteristics of patients with gynaecologic malignancies and participants of the control group.*

	Age (years)	Parity (%)	Smoking (%)	Premenopausal (%)	Postmenopausal (%)	Weight (kg)	BMI (kg/m^2)
Control group n=152	53.2±12.1	Primi 78% - multi 22%	75.7%	25.5%	74.5%	66±12.8	25.2±4.5
Breast cancer n=65	54.1±11.5	Primi 65% - multi 35%	76.4%	26.5%	73.5%	67±11.2	24.9±4.7
Encometrial cancer n=49	55.3±10.3	Primi 68% - multi 32%	77.2%	27.2%	72.8%	70±10.7	24.6±4.2
Ovarian cancer n=35	58.4±14.8	Primi 56% - multi 44%	78.1%	26.8%	73.2%	68±10.5	25.2±4.5
Vulvar cancer n=3	69.5±2.5	Multi 100%	0%	0%	100%	69±13.1	24.9±4.1
p-value*	0.115	0.321	0.121	0.129	0.324	0.323	104

**p-value controls vs. all cancer patients*

Table 2. — *Histologic subtypes, duration of surgery, and bleeding loss in gynaecological cancer patients and participants of the control group.*

	FIGO/TNM Stage		Histological subtypes	Operation time [Min.] (med±SD)*	Blood loss [ml] (med±SD)
Breast cancer n=65 (TNM)	Ia-c	n=35	Ductal G1-2 n=56	106±19*	75±15
	IIa-c	n=21	Lobular G2-3 n=9		
	III	n=7			
	IV	n=2			
Endometrial cancer n=49 (TNM)	Ia-c	n=40	Adenocarcinoma G1-2 n=38	276±35	225±25
	IIa-c	n=9	Endometroid G2-3 n=7		
			Undifferentiated n=2		
Ovarian cancer n=35 (FIGO)	Ia-c	n=27	Serous n=26	276±35	225±25
	IIa-c	n=5	Mucinous n=2		
	III	n=3	Endometroid n=3		
			Undifferentiated n=2		
Vulvar cancer n=3 (TNM)	Ib	n=3	Platt-Ca. n=2	276±35	225±25
Controls n=152	Myoma n=89		Adenomyosis n=22	124±15*	95±10
			Uterus myomatosus n=67		
	Benign ovarian tumors n=32		Endometriosis cysts n=9		
			Serous n=19		
			Mucinous n=4		
	Benign breast tumors n=31		Breast fibroma n=23	44±10	25±10
			Breast cysts n=8		

**Including waiting times for results of intraoperative histological evaluation in patients with benign tumor disease and breast cancer patients i.e. tumor margins, lymph node involvement; p-value compared to controls < 0.001*

Table 3. — *Laboratory findings (blood count, red blood cell indices, hemostaseological parameters) in gynaecological and breast cancer patients compared to healthy controls with benign gynaecological tumors before and after primary surgery.*

	Day	Hbg/dL	HCT%	Plt 103/µL	Fibmg/dL	MCV fL	MCHpg	MCHC g/dL	APTTS	Protein g/dl	Alb g/dl	Alb/Glob ratio	D-Dimer ng/ml ()	ESR mm/h
H.C.	0	11.2	36.4	224.1	221	77.6	29.2	26.1	26.4	6.6	4.9	1.8	195	16
	1	10.9	33.8	220.2	220	77.9	29.8	26.3	26.8	6.4	4.8	1.6	194	15
	3	10.9	33.9	219.0	224	76.9	29.9	26.6	26.4	6.5	4.7	1.5	193	14
	5	11.2	33.8	225.4	228	77.4	29.8	26.5	26.5	6.7	4.8	1.6	196	12
E.C.	0	12.6*	35.1*	199.3*	245*	89.4*	30.2*	29.7*	26.8*	6.9*	4.6*	1.6*	288*	55*
	1	11.6#++	32.8#++	198.2#++	242#++	92.3#+	31.6#	30.1#+	27.9#	6.5#+	4.2#+	1.3#+	390#+	58#+
	3	11.9#++	32.9#++	170.4#++	268#++	93.6#+	31.8#+	31.4#+	28.5#+	6.9#	4.8#+	1.2#+	420#+	59#
	5	11.8#++	32.1#++	290.5#++	470#++	95.2#+	33.4#+	31.5#+	31.4#+	6.9#	4.7#+	1.2#+	450#+	44#+
O.C.	0	11.6*	31.5*	250.3*	290*	90.4*	27.3*	30.1*	29.7*	5.9*	4.5*	1.4*	350*	87*
	1	10.6#++	30.1#++	247.4#++	288#	91.8#+	26.7#+	30.9#	30.7#	6.3#+	4.7#	1.2#	390#+	74#+
	3	10.7#++	29.9#++	190.4#++	457#++	94.5#+	28.1#	31.4#+	35.6#+	6.6#+	4.8#	0.9#	450#+	89#+
	5	10.9#+	29.8#+	440.1#	528#++	95.6#+	28.3#+	31.9#+	36.2#+	6.7#+	4.9#+	0.8#	499#+	95#
V.C.	0	10.2*	30.2*	220.1*	249*	80.4*	27.2*	26.7*	25.4*+	5.8*	4.1*	1.8*	230*	56*
	1	9.8#	28.2#	200.2#	245#+	82.7#+	28.1#	29.1#+	26.1#	6.2#	3.8#	1.67#	234#+	54#+
	3	9.9#	29.2#	140.3#	256#	88.7#	29.4#	30.4#+	27.8#	6.1#	3.9#	1.45#	257#+	57#
	5	10.1#	30.1#	255.250#	259#	89.1#	30.2#	31.9#+	29.3#	6.4#	4.2#+	1.39#	290#+	67#
B.C.	0	13.1*	39.4*	255.4*	265*	86.5*	28.2*	29.1*	27.2*	6.1*+	4.7*	1.7*	295*	56*
	1	12.5#++	37.1#++	205.2#++	258#++	87.1#+	28.8#+	28.9#	29.8#+	6.3#+	4.9#	1.4#	360#+	59#
	3	12.7#++	37.5#++	250.5#++	298#++	87.5#+	28.4#+	29.4#+	30.2#+	6.2#+	4.8#+	1.2#	398#+	55#+
	5	12.9#+	38.4#+	297.3#++	450#++	93.2#+	29.2#+	30.7#+	34.5#+	6.4#+	4.7#	0.9#	487#+	49#+

**Day: 0 = day before surgery, 1= first postoperative day, 3 = third postoperative day, 5 = fifth postoperative day*
 # p-value controls vs. all cancer patients preoperatively + p-value before vs day 1, day 3 and day 5: +p < 0.05; ++p < 0.001.
healthy controls = HC, endometrial cancer = EC, ovarian cancer = OC, vulvar cancer = VC, breast cancer = BC.

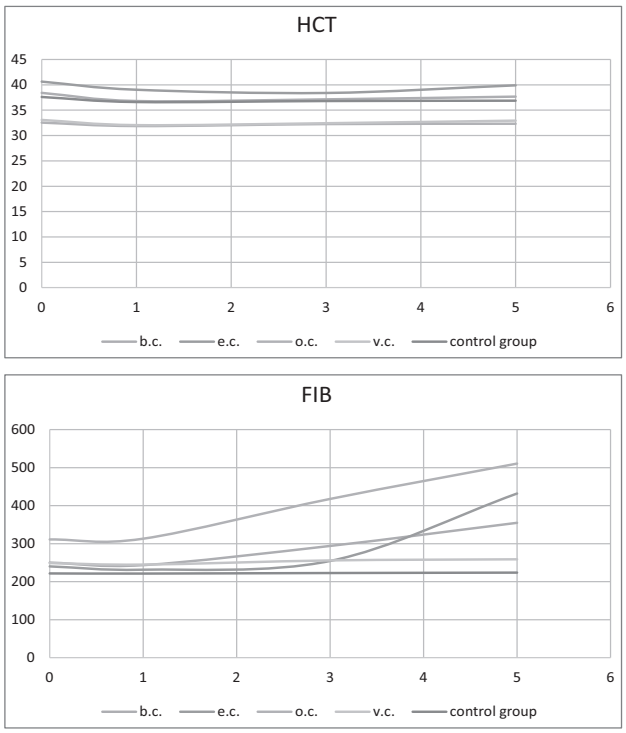

Figure 1. — Hematocrit and fibrinogen concentrations before and after surgery. Day: 0 = day before surgery, 1 = first postoperative day, 3 = third postoperative day, 5 = fifth postoperative day.

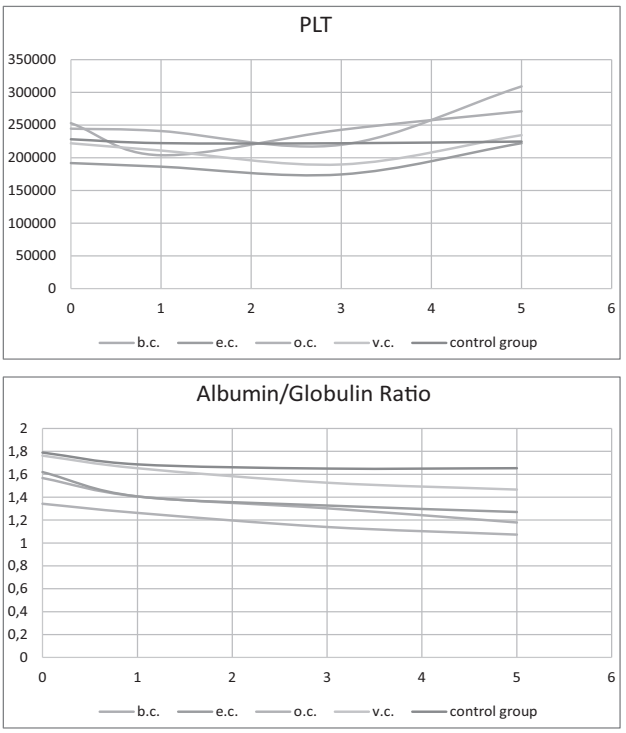

Figure 2. — Platelet count and albumin/globulin ratio before and after surgery. Day: 0 = day before surgery, 1 = first postoperative day, 3 = third postoperative day, 5 = fifth postoperative day.

was lowest (Table 3).

Mean fibrinogen concentrations temporarily decreased on day 1 and increased on the third day postoperatively (Figure 1). The platelet count was unchanged in the control group while aside from breast cancer patients, the number was temporarily and statistically significantly lowest on the third postoperative day in all cancer types. (Figure 2). No statistically significant changes were noticed in the total protein and albumin concentrations. The albumin/globulin ratio markedly and continuously decreased in all cancer patients postoperatively, which was statistically significant in endometrial and breast cancer patients by a reduction to up to 47% (Figure 2). D-dimer concentrations were barely unchanged after the surgery, but the concentrations were higher in cancer patients than in those with benign disease (Figure 3). Activated partial thromboplastin time was slightly prolonged in the cancer patients preoperatively with increasing clotting times postoperatively, while it was unaffected in patients undergoing surgery for benign tumor disease.

Postoperatively, mean MCV increased statistically significantly in all cancer patients and remained higher until the fifth day within each cancer group. There was a trend towards a higher MCHC postoperatively in the cancer patients which however was not statistically significant. None of the red blood indices tended to statistically significantly change after surgery for benign disease. None of the laboratory parameters was correlated with the aforementioned demographic data in neither cancer patients nor women of the control group. None of the mean laboratory results were out of the normal range in neither the cancer nor in the control group. In none of the subjects of the preset study were there clinical symptoms suspicious of deep vein thrombosis or pulmonary embolism until the fifth postoperative day

Discussion

Measurable pathological changes in hemostasis occur in about 60% of cancer patients and cancer growth is associated with the development of an extending hypercoaguable state that is the result of several coincidental mechanisms such as mucin release by tumor cells, exposure of tissue factor rich surfaces on the neoplastic cells and endothelium, release of tissue factor bearing microparticles, expression of tumor cell located thrombin initiating cysteine proteinase, and hypoxia induced by impaired blood flow in the tumor microcirculation [2, 5]. The extent of surgical intervention, length of operating time, postoperative immobility, and length of hospital stay is related to the tumor stage, and thus according to prior studies is a significant risk factor for VTE [16]. Generally the combination of thrombosis and cancer is associated with a higher mortality risk and worse

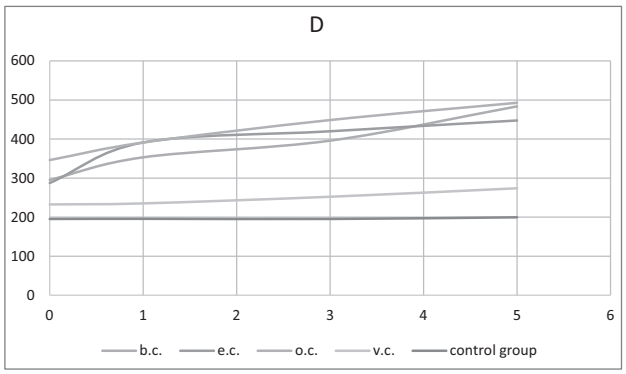

Figure 3. — D-Dimer concentrations before and after surgery. Day: 0 = day before surgery, 1 = first postoperative day, 3 = third postoperative day, 5 = fifth postoperative day.

prognosis [1, 17]. In cancer patients the presence of genetic thrombophilia, most commonly Factor Leiden V and Prothrombin 20210A mutation signal a particular high risk for thrombosis [1].

Although several studies have found marked differences in the preoperative laboratory findings including coagulation markers within cancer patients compared to patients undergoing surgery for non-malignant indications, none of these laboratory markers has ever proved to sufficiently identify patients at high risk for postoperative thrombosis. In the current study none of the patients developed clinical overt thrombosis, therefore laboratory results were not assessable for this

Thrombosis according to some prior reports is irrespective of cancer stage, however Chew *et al.* found that the VTE incidence has the highest value during the first few months after the diagnosis in advanced stage cancer [14, 18-20]. The risk of recurrent thrombosis is greater in patients with cancer compared to those with benign diseases [21]. It has been reported that the main laboratory parameters that lead to coagulation activation have an increased susceptibility to VTE like whole–blood plasma viscosity (WPV), plasma viscosity (PV), HCT, fibrinogen, D-dimers, platelets, and A/Gl-R.The balance of these hemostaseologic parameters represent physiological autoregulation for the maintenance of oxygen delivery in the vessel microcirculation [7].

High PV is an important contributor to decrease in perfusion and oxygenation of tumor tissue [7]. Hypoxia favors thrombosis and promotes tumor cell proliferation [14]. Thrombocytosis is observed in cancer patients, associated with tumor progression, while the depletion has a relative antimetastatic effect [22, 23]. The reason of the malignancy association with thrombocytosis is the interleukin-6 (IL-6) effect to potently promote megakaryocyte maturation and enhance platelet production [22-24]. D-dimer is a thrombogenic and angiogenic marker, a degraded product of fibrin generation [25, 26]. Its presence reflects the activation of the coagulation-fibrinolysis system, is associated with clinical tumor growth, invasion, metastasis, and elevated levels are predictive of recurrent VTE in cancer patients [12, 27]. PV is influenced by the presence of macroglobulins, total protein, and cholesterol and correlate significantly with fibrinogen level, red blood aggregation, and all these parameters are increased in various diseases especially in cancer cases as a reflection of the overall stress response of cancer patients and dehydration [3, 15]. Increased PV results in the development of fibrin-thrombin formation and stimulation of coagulation factors and signals [15]. High fibrinogen concentrations can lead to a non-specific and reversible binding of fibrinogen and red blood cell membrane glycoproteins inducing red blood cells aggregation, decreased cell deformability, and reduction of the oxygen transport capacity [8]. Increased fibrinogen level and reduced A/Gl-R is pronounced in ovarian cancer cases based on the high ovarian tumor volume and has the lowest values in endometrial cancer cases with the smallest volume. In cases of breast cancer the A/Gl-R is significantly increased and subsequently the PV is lower than the pelvic gynaecological cancer [28]. According to prior studies, total protein concentrations, albumin, and immunglobulins remain normal or slightly increased and correlate only moderately with PV [8].

The present authors found that a significant rise in PV according to the results based on fibrinogen, d-dimers and platelets increase, and A/Gl-R moderate decrease postoperative reflect the importance of tumor volume (ovarian cancer highest from pelvis-cancers, lowest in breast cancer), and disease status. Biological features of ovarian cancer cells possible increase the production of fibrinogen [29]. None of the demographical parameters was associated to the examined haemostasiologic parameters.

In the present study population, ovarian cancer patients were identified as the subgroup with the highest risk for postoperative thrombosis. The most striking finding of the present study was the strong association between gynaecological cancer and the changes of the haemostasiologic parameters in the early postoperative period. However, in the present study, haemostasiologic parameters did not differ significantly between the two groups. No significant difference of the haemostasiologic parameters arose among the cancer subgroups either. Thrombosis occurred in neither group. All the important coagulation tests have been performed in the present study [30]

Conclusion

The present findings are limited to some trends without a clear take home message for clinical approved protocols, however the results corroborate with those from other previously published reports [8, 9 ,26, 28]

Further randomized clinical trials with more patients are

necessary to investigate differences between disease stages, other factors like regulatory proteins and proangiogenic endothelial growth factors, and to determine whether thromboprophylaxis reduces the risk of thromboembolic complications.

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