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Plasma fibrinogen levels in patients with benign and malignant ovarian tumors

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HIGHLIGHTS

- Plasma fibrinogen levels and CA 125 are independently associated with ovarian cancer.
- In patients <50 years, plasma fibrinogen levels can help in the differential diagnosis of ovarian tumors.
- Advanced tumor stage in ovarian cancer is associated with higher plasma fibrinogen levels.

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ABSTRACT

Objective. Plasma fibrinogen is a key acute phase protein and known to be elevated in ovarian cancer. We aimed to investigate the association between plasma fibrinogen and malignant and benign ovarian tumors.

Methods. In a retrospective, single-center study, we evaluated preoperative plasma fibrinogen levels in 471 patients with benign and in 224 patients with malignant (borderline ovarian tumor [BOT]: n = 36, epithelial ovarian cancer [EOC]: n = 188) ovarian tumors. The association between preoperative plasma fibrinogen levels and clinico-pathological parameters was investigated. A multivariate logistic regression model was performed to identify an independent association.

Results. Mean (standard deviation) preoperative plasma fibrinogen levels in patients with benign ovarian tumors, BOT, and invasive ovarian cancers were 346.7 (99.7), 372.8 (114), and 472.6 (148.4) mg/dL, respectively ($p < 0.001$). Within the EOC cohort, patients with advanced stage disease had higher plasma fibrinogen levels (485.5 [151.3] mg/dL) than patients with early stage disease (430.9 [130.3] mg/dL; $p = 0.03$). In a multivariate model plasma fibrinogen was identified to be independently associated with the presence of BOT and EOC. In the subgroup of patients <50 years, plasma fibrinogen levels remained independently associated with malignant ovarian tumors in CA 125 positive and negative patients.

Conclusion. Plasma fibrinogen levels are independently associated with malignant ovarian tumors. Plasma fibrinogen levels showed an independent association with malignant ovarian tumors in the subgroup of patients <50 years, in whom differential diagnosis of ovarian tumors is particularly challenging.

Introduction

Fibrinogen, the coagulation factor I, is a soluble, large, complex glycoprotein mainly synthesized by hepatocytes [1,2]. During normal blood coagulation, thrombin converts the soluble fibrinogen into insoluble fibrin strands, leading to clot formation at the end of the coagulation pathway [1]. Besides its essential function in the coagulation cascade, fibrinogen represents one of the major acute phase proteins, and its biosynthesis increases with inflammation and stress [3,4]. Therefore, elevated plasma fibrinogen levels can be detected during the acute phase of the inflammatory response [5] and can serve as additional markers for various inflammatory processes.

Regarding malignant diseases, elevated plasma fibrinogen levels are not specific for any malignancy, as they have been observed in patients with colon cancer, hepatocellular carcinoma, malignant pleural mesothelioma, and ovarian cancer and have been identified to serve as independent prognostic parameters in these malignancies [6–10]. In ovarian cancer, elevated plasma fibrinogen levels have also been found to be

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predictive for a higher rate of non-optimal cytoreduction and a poorer response to chemotherapy [11].

Ovarian tumors are frequently encountered in symptomatic, but also in asymptomatic women of all ages [12,13]. The differential diagnosis of an adnexal mass is notoriously difficult. The goal of evaluation is not only to differentiate between benign and malignant conditions, in order to avoid unnecessary surgical procedures, but also to refer patients with a high grade of suspicion for a malignant adnexal mass to a specialized gynecologic oncology unit. In current clinical practice, transvaginal ultrasonography, physical examination, and serum measurements of CA-125 are used for risk assessment [14–17]. In contrast to the technique of transvaginal ultrasonography, which is usually an examiner- and experience-dependent procedure, tumor markers have the advantage to serve as easily reproducible, objective parameters for the differential diagnosis of ovarian tumors.

Therefore, a number of tumor markers have been tested for their potential to further individualize the clinical management of women with ovarian tumors, such as vascular endothelial growth factor (VEGF), cancer antigen (CA) 72-4, monocyte chemoattractant protein-1, CYFRA 21-1, and human epididymal protein (HE)-4 [18–22]. Several factors involved in inflammation and coagulation such as C-reactive protein (CRP), D-dimer, thrombopoietin, and serum tissue factor have been shown to potentially serve as additional parameters for the differential diagnosis of ovarian tumors [23–25].

As fibrinogen is one of the most prominent proteins involved in inflammation and the coagulation pathway [26], and its measurement is routinely performed in most clinical laboratories worldwide, the aim of the present study was to examine the potential of plasma fibrinogen levels as an additional marker in the differential diagnosis of patients with ovarian tumors.

Materials and methods

Patients

A series of 695 consecutive patients with ovarian tumors, i.e., epithelial ovarian cancer (EOC), borderline ovarian tumors (BOTs), and benign ovarian tumors, were included in the present study. The institutional review of the Medical University of Vienna board approved the present study (IRB number: 1958/2013). All patients were treated at the Department of General Gynecology and Gynecologic Oncology, Gynecologic Cancer Unit, Comprehensive Cancer Center, Medical University of Vienna, Austria, between February 1996 and December 2004.

Prior to elective surgery a physical examination was performed, body temperature was measured, and respective blood tests were performed. As inflammatory diseases are known to be associated with elevated plasma fibrinogen levels, patients with any acute inflammatory condition were excluded from the present study. Patients with any coexisting malignancy were also excluded. Patients were treated according to standards of our institution undergoing laparoscopy or laparotomy with cystectomy or salpingoophorectomy. Patients with EOC or BOT were treated with hysterectomy, bilateral salpingo-oophorectomy, pelvic and/or paraaortic lymphadenectomy, appendectomy, omentectomy and cytoreductive procedure in order to resect all gross tumors.

Fibrinogen measurement

As a part of the clinical routine, blood samples (citrated plasma) for evaluation of plasma fibrinogen levels were obtained by peripheral venous puncture 24–48 h prior to surgery. Plasma fibrinogen levels were determined by the Clauss method [27], using clotting reagents from Diagnostica Stago (Asnieres, France). The manufacturer claims an intra-assay variability of 3.5%. Plasma fibrinogen levels of 180–390 mg/dL were defined as normal.

Statistics

Values are given as means (standard deviation [SD]) or medians (25th, 75th percentiles). Parameters were compared between two or more than two groups using t-tests and one-way ANOVA, respectively. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using a 2×2 table with a chi-square test for serum CA 125 alone (<35 U/mL vs. ≥ 35 U/mL), plasma fibrinogen alone (<390 mg/dL vs. ≥ 390 mg/dL), and for two clinical scenarios: 1st scenario: both markers positive, 2nd scenario: one or the other positive.

The diagnostic value of plasma fibrinogen to discriminate between malignant (EOC and BOT) and benign ovarian tumors was further assessed using univariable and multivariable logistic regressions comprising plasma fibrinogen (<390 mg/dL vs. ≥ 390 mg/dL), serum CA 125 (<35 U/mL vs. ≥ 35 U/mL), and patients' age (calculated in decades) as independent parameters. The diagnostic value of plasma fibrinogen levels was further evaluated by constructing a receiver-operator characteristics (ROC) curve using sensitivity (true positive rate) and 1-specificity (false positive rate) resulting from assuming various cut points of plasma fibrinogen. P-values <0.05 were considered statistically significant. For all statistical analyses we used the SPSS statistical software system v9.2 (SAS Institute Inc. Chicago, IL).

Results

We included 224 patients with malignant ovarian tumors (188 patients with EOC, 36 patients with BOT), and 471 patients with benign adnexal tumors in the present study. Mean (SD) age of patients with benign ovarian tumors, BOT, and EOC was 46.6 (16.2), 49.4 (15.2), and 60.8 (13.6), years, respectively ($p < 0.001$). Median (25th, 75th percentiles) serum CA 125 in patients with benign ovarian tumors, BOT, and EOC were 38.4 (90.7), 137.5 (159.9), and 2409.4 (8930.6) U/mL, respectively ($p < 0.001$). Final histologic results of the benign ovarian tumors were: endometrioma: $n = 73$, sactosalpinx: $n = 20$, serous cystadenoma: $n = 128$, mucinous cystadenoma: $n = 57$, teratoma: $n = 55$, fibroma: $n = 14$, and functional ovarian cyst: $n = 124$.

Mean (SD) preoperative plasma fibrinogen levels in patients with benign ovarian tumors, BOT, and EOC were 346.7 (99.7), 372.8 (114), and 472.6 (148.4) mg/dL, respectively ($p < 0.001$). Table 1 shows

Table 1
Plasma fibrinogen levels in patients with epithelial ovarian cancer (EOC) and borderline ovarian tumors (BOTs) broken down by clinico-pathologic parameters.

	Number	Fibrinogen plasma levels (mg/dL)*	p-Value
Patients with EOC/BOT	224	456.5 (147.8)	–
Tumor stage			
FIGO I	31	436.5 (119.2)	0.03^
FIGO II	15	419.9 (154.1)	
FIGO III	113	486.1 (155.8)	
FIGO IV	29	483.2 (134.3)	
Tumor grade			
G1	26	465.1 (140.0)	0.9^
G2	60	465.5 (150.5)	
G3	102	477.7 (154.3)	
Histological type			
Serous	126	469.7 (150.4)	0.9^
Mucinous	14	484.4 (128.3)	
Endometrioid	29	467.2 (154.8)	
Others	19	478.1 (136.0)	
Age			
≤50 years	46	455.1 (147.7)	0.4†
>50 years	142	478.3 (148.7)	

* Values are given as means (standard deviation).
^ p-Values were calculated using one-way ANOVA.
† p-Value was calculated using a t-test.