EJGO European Journal of Gynaecological Oncology

Plasma fibrinogen, CRP, and hs-CRP levels in patients with benign and borderline ovarian tumours

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Summary

Objective: Ovarian tumours can be classified as benign, borderline or malignant lesions. The purpose of this study was to assess, *inter alia*, fibrinogen concentration, and the (C-reactive proteins) and high-sensitivity CRPs (hs-CRPs) levels in the blood serum of patients with ovarian lesions. *Study Design:* The study involved patients treated laparoscopically and laparotomy in the Gynaecology and Obstetrics Clinical Hospital of the Poznan due to adnexal changes in the form of endometrial cysts and mature teratomas, mucinous cysts, borderline tumors of the ovary, simplex (serosa) cysts or haemorrhagic cysts. *Results:* The groups differed considerably in fibrinogen ($p = 0.022$) and d-dimer levels ($p = 0.002$). *Conclusion:* Statistically significant differences were found in the fibrinogen and d-dimer profiles among patients with benign and borderline ovarian tumours. However, this requires further investigations in larger patient groups.

Key words: Fibrinogen; CRP; hs-CRP; Ovarian tumours.

Introduction

Cancerous ovarian tumours can be classified as benign, borderline or malignant lesions. They occur at various ages, though usually between the ages of 30 and 60 years, developing either from the ovarian stroma or germinal epithelium [1, 2]. In women of reproductive age, benign tumours or cysts (i.e. serosa cysts, mucinous cysts, endometrial cysts and mature teratomas) constitute the majority of ovarian lesions. Endometriosis is an estrogen-dependent chronic disease which involves immunological and inflammatory implantation and the growth of the endometrium outside the uterus. Endometriosis most frequently takes the form of endometrial cysts, commonly referred to as chocolate cysts because they contain a thick brownish fluid [3, 4]. Mature teratomas (*teratomata adultum*) account for over 95% of all ovarian teratomas, being one of the most frequent types of ovarian cancer, and for over 58% of benign ovarian lesions. Although 80% of mature teratomas develop in women of reproductive age, most often during their twenties and thirties, these kinds of tumours can also occur before reaching sexual maturity [5]. Teratomas result from primary embryonic cell pathologies. Multi-cellular tumours contain mainly skin or hair elements, although such constituents as fatty, cartilaginous, neural, osseous or lung tissues, and teeth or GI tract tissues are also found within such lesions, though less frequently [5]. Simplex (serosa) cysts are very common single-celled unilateral lesions with a diameter ranging from 3 to more than 8 cm. They are filled with non-reabsorbed follicular fluid and covered by immature ovarian follicle epithelium. They contain a transparent and usually light fluid; however, when a blood vessel rupture occurs within the cyst wall, they may evolve into haemorrhagic cysts, similar to other tumour-like lesions. As they usually give no symptoms, most of them remain undiagnosed and are spontaneously reabsorbed or may rotate around the ovarian pedicle [6].

Malignant cancerous ovarian tumours, in turn, constitute a heterogeneous group of diseases. The incidence of malignant ovarian tumours in women of reproductive age does not exceed a few percent of all ovarian tumours, and these are mainly lesions of epithelial or germinal origin at low stages of progression [7, 8].

Diagnostic tests of ovarian lesions include physical examination and ultrasonographic assessment, along with determining biochemical markers, including mainly CA-125 and HE4. In recent years, literature sources have indicated the significance of fibrinogen and C-reactive proteins (CRPs) in diagnosing malignant ovarian cancer. Therefore, the purpose of this study was to assess, *inter alia*, fibrinogen concentration, and the CRP and high-sensitivity CRPs (hs-CRPs) levels in the blood serum of patients with ovarian lesions.

Materials and Methods

The study involved patients treated laparoscopically and/or laparotomy in the Gynaecology and Obstetrics Clinical Hospital of the Poznan Medical University due to adnexal changes in the form of endometrial cysts and mature teratomas, mucinous cysts, bor-

Revised manuscript accepted for publication March 21, 2017

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XL, n. 1, 2019
doi: 10.12892/ejgo4175.2019

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derline ovarian tumours, simplex (serosa) cysts or haemorrhagic cysts, in the period from September 2012 to December 2014.

Patient enrolment methods and ways of obtaining the research material and its storage had been previously approved by the Bioethics Committee at the Poznan University of Medical Sciences (specifically approved only for this study of 8 January 2009; Resolution No. 10/2009). The patients gave written obtained consent for this study. Ethics committees approved this consent procedure.

Qualification criteria included: intraoperative diagnosis of an endometrial cyst without macroscopic peritoneal endometriosis and/or ovarian tumours in the form of: mature teratoma, mucinous cysts, borderline ovarian tumours, simplex (serosa) cysts or haemorrhagic cysts, unremarkable obstetric history, and good health without comorbidities. The patients had not been previously treated for infertility. Preoperative laboratory tests did not demonstrate any coagulation abnormalities. In all the patients with endometrial cysts, mature teratomas, mucinous cysts, simplex (serosa) cysts or haemorrhagic cysts, laparoscopy was performed in the first phase of the cycle. In all the patients with borderline ovarian tumours, laparotomy with hysterectomy and adnexectomy was performed.

The criteria for exclusion from the study were: coexistence of various ovarian lesions in one patient (e.g. an endometrial cyst and mature teratoma), history of obstetric complications, and coagulation disorders.

After intraoperative histopathological verification of the obtained tissue fragments, the patients were divided into six study groups. Group E (endometrial cysts) included women with histologically confirmed endometrial cysts (n = 11), without macroscopic foci of peritoneal endometriosis. Group T (mature teratoma) comprised patients after laparoscopic treatment of ovarian mature teratomas (n = 11). Group M (mucinous cysts) comprised patients after laparoscopic treatment of a mucinous cyst (n = 6). Group borderline ovarian tumours (BOT) comprised patients after laparotomy treatment for borderline ovarian tumours (n = 17). Group S (simplex (serosa) cysts) comprised patients after laparoscopic treatment of ovarian simplex (serosa) cysts (n = 19). Group H (haemorrhagic cyst) comprised patients after laparoscopic treatment of a haemorrhagic cyst (n = 5).

The study was conducted using laboratory assays and a survey (questionnaire). Blood samples were obtained on admission to hospital, i.e. the day before the surgery, in the morning, on an empty stomach. Concentrations were determined in pg/mL, as mean ± SD (standard deviation) and median (Me). The Kruskal-Wallis One Way Analysis of Variance on Ranks correlation coefficients were calculated to assess the relationships between individual variables and the power of these relationships. The significance level assumed for all tests was $p \leq 0.05$. Statistical calculations were made using the STATISTICA software.

Results

Group E comprised patients after the laparoscopic treatment of endometrial cysts (n = 11), without macroscopic foci of peritoneal endometriosis, aged 34.27 ± 13.54 years, Me = 31 years with a 5.32 ± 1.96-cm lesion in the right ovary or with a 5.26 ± 3.18-cm lesion in the left ovary. Group T comprised patients after the laparoscopic treatment of ovarian mature teratomas (n = 11), aged 32 ± 6.74 years, Me = 30 years with a 4.96 ± 3.12-cm lesion in the right ovary or with a 5.57 ± 3.47-cm lesion in the left ovary. Group M (mucinous cysts) comprised patients after the laparoscopic treatment of mucinous cysts (n = 6), aged 46.74 ± 13.71 years, Me = 44 years with a 6.32 ± 3.57-cm lesion in the right ovary or with a 6.89 ± 2.52-cm lesion in the left ovary. Group BOT comprised patients after treatment for borderline ovarian tumours without macroscopic foci of carcinomatosis (n = 17), aged 61.12 ± 12.24 years, Me = 59 years with a 7.91 ± 3.64-cm lesion in the right ovary or with an 11.11 ± 1.41-cm lesion in the left ovary. Group S (simplex (serosa) cysts) comprised patients after the laparoscopic treatment of ovarian simplex (serosa) cysts (n = 19, aged 43.00 ± 14.48 years, Me = 46 years with a 5.63 ± 2.21-cm lesion in the right ovary or with a 6.12 ± 4.34-cm lesion in the left ovary. Group H (haemorrhagic cyst) comprised patients after the laparoscopic treatment of haemorrhagic cysts (n = 5), aged 31.8 ± 7.53 years, Me = 33 years with a 5.85 ± 0.64-cm lesion in the right ovary or with a 3.70 ± 0.56-cm lesion in the left ovary.

The concentration of various blood count and coagulation system parameters, as well as the CRP and hs-CRP levels, are shown in Tables 1, 2, and 3. The groups differed considerably in fibrinogen (p=0.022) and d-dimer levels (p = 0.002), although the test of multiple comparisons (using Dunn's method) indicated a statistically significant difference ($p < 0.05$) only between groups with mucinous cysts and groups with epithelial ovarian cancer.

Discussion

Fibrinogen belongs to a group of acute-phase proteins having a delayed increase in concentration in relation to CRP, whose concentration rises, *inter alia*, during chronic inflammatory processes. Determined together with hs-CRPs, it is useful when assessing the risk of cardiovascular diseases. Along with the acute-phase protein function, the fibrinogen participates in the coagulation system processes, with reference values ranging from 2 to 4 g/l. Hefler-Frischmuth K *et al.* in a retrospective, single-centre study, evaluated the preoperative plasma fibrinogen levels in patients with benign and with malignant, BOTs, and with epithelial ovarian cancer (EOC) [9]. They observed that plasma fibrinogen levels were independently associated with malignant ovarian tumours, while plasma fibrinogen levels showed an independent association with malignant ovarian tumours in the subgroup of patients <50 years. Polterauer *et al.* analysed the pretherapeutic plasma fibrinogen levels as a prognostic parameter in patients with EOC, observing that elevated plasma fibrinogen levels were associated with advanced stages of the tumour and the presence of a postoperative residual tumour mass, but not with histological grade and histological type [10]. In turn, Grabowski *et al.* analysed the blood coagulation parameters in patients treated surgically for endometrial cysts, in comparison to the control group diagnosed with benign ovarian tumours. In patients suffering from endometriosis, a

Table 1. — *Levels of other agents in blood serum of patients with benign and borderline ovarian tumours.*

Group		WBC [G/l]	RBC [T/l]	PLT [G/l]	HGB [mmol/l]	HCT
E	Mean ±SD	6.90±2.27	4.42±0.31	268.67±88.86	7.96±0.55	38.98±2.30
n=11	median	6.15	4.35	280	8.2	39.3
T	Mean ±SD	7.45±3.44	4.48±0.25	295.82±68.04	7.96±0.49	38.55±2.25
n=11	median	6.62	4.49	258	8	38.9
M	Mean ±SD	7.00±2.39	4.49±0.27	276.37±83.037	8.16±0.61	39.98±2.54
n=6	median	7.18	4.43	262	8,2	40.2
BOT	Mean ±SD	7.31±2.99	4.29±0.58	254.65±129.22	7.70±0.98	37.81±4.39
n=17	median	6.37	4.32	274	7.08	38.5
S	Mean ±SD	6.71±1.47	4.58±0.32	304.00±41.81	8.12±0.71	39.55±2.85
n=19	median	6.75	4.62	301.5	8.1	40.05
H	Mean ±SD	8.09±1.76	4.81±0.34	267.50±84.90	8.55±0.84	41.05±3.21
n=5	median	7.78	4.86	263	8.65	41.15
*p**		0.863	0.324	0,848	0.281	0.276

** p < 0.05 Kruskal-Wallis One Way Analysis of Variance on Ranks*

Table 2. — *Levels of other agents coagulology in blood serum of patients with benign and borderline ovarian tumours.*

Group		APTT	PT	INR	PI	F	D-d
E	Mean ±SD	30.47±2.29	13.8±0.3	1.05±0.04	95.23±3.56	3.11±0.11	220±0.11
n=11	median	31.2	13.8	1.05	95.6	3.1	220
	C.I. of Mean	5.69	0.75	0.10	8.85	0.56	0.67
T	Mean ±SD	29.67±1.36	13.33±0.51	1.02±0.04	97.60±4.16	4.21±0.44	470.12±180.83
n=11	median	29.2	13.2	1	100	4.4	450
	C.I. of Mean	3.38	1.28	0.1	10.33	1.08	449.21
M	Mean ±SD	30.34±2.40	14.35±1.25	1.09±0.10	91.33±7.39	3.15±0.62	826.15±1820.03
n=6	median	30	13.9	1.06	94.2	2.8	220
	C.I. of Mean	1.45	0.753	0.0554	4.466	0.377	1099.833
BOT	Mean ±SD	28.83±3.74	14.45±1.17	1.11±0.08	90.38±6.58	3.73±1.11	2586.00±3584.13
n=17	median	28.15	14.4	1.105	90.2	3.75	1325
	C.I. of Mean	1.99	0.62	0.04	3.51	0.59	1909.85
S	Mean ±SD	29.92±1.76	13.52±0.25	1.04±0.02	95.78±1.53	3.11±0.65	229.23±17.54
n=19	median	30.2	13.4	1.04	96.3	3.2	220
	C.I. of Mean	3.28	0.42	0.03	2.93	1.23	31.82
H	Mean ±SD	29.40±1.41	15.45±3.18	1.19±0.23	85.30±17.54	2.90±0.85	220±12.11
n=5	median	29.4	15.45	1.185	85.3	2.9	220
	C.I. of Mean	12.71	28.59	2.10	157.56	7.62	0.38
*p**		0.220	0.292	0.271	0.362	0.022*	0.002*

** p < 0.05 Kruskal-Wallis One Way Analysis of Variance on Ranks. APTT: activated partial thromboplastin time, PT: prothrombin time, INR: international normalized ratio, PI: prothrombin index, F: fibrinogen, D-d: D-dimer.*

Table 3. — *Levels of CRP and hs-CRP in blood serum of patients with benign and borderline ovarian tumours.*

Group		CRP	hs-CRP
E	Mean ±SD	1.97±0.12	2.03±2.26
n=11	median	0.97	0.88
T	Mean ±SD	1.72±1.52	1.86±2.63
n=11	median	0.78	0.84
M	Mean ±SD	2.98±0.97	2.60±3.00
n=6	median	1.8	1.6
BOT	Mean ±SD	6.21±1.43	5.44±4.11
n=17	median	6.12	5.06
S	Mean ±SD	3.11±1.83	2.15±2.18
n=19	median	1.85	1.75
H	Mean ±SD	2.79±1.56	2.47±2.24
n=5	median	0.83	0.61
*p**		0.098	0.079

** p < 0.05 Kruskal-Wallis One Way Analysis of Variance on Ranks*

slightly increased average plasminogen and α2-antiplasmin concentration was found, along, with lower concentrations of the plasminogen-1 activator inhibitor and reduced activity of the tissue plasminogen activator. The authors suggest that the reference changes occurring within the fibrinolytic system often seem contradictory. This finds support in the mechanism of formation of the focal points of endometriosis being complex and still unexplained [11]. In turn, Bromboszcz *et al.* [12] observed that increased fibrinolytic blood activity, with a simultaneous reduction in fibrinogen concentration, was a major deviation in the haemostatic system found in patients suffering from endometriosis. Having assessed fibrinogen concentration in the blood serum of patients with endometrial cysts, with no coexistent focal points of peritoneal endometriosis, in comparison to patients with teratomas, the present authors observed statisti-

cally significant differences between these two groups (cysts *vs*. teratomas, 3.12 *vs*. 2.57 mg%, respectively; $p < 0.001$) [13].

The CRP is one of the most important acute-phase proteins routinely measured in clinical laboratories as a marker for various acute and chronic inflammatory diseases [14]. CRP is a systemic marker of inflammation, while epidemiological evidence consistently supports an association between elevated CRP and the risk of epithelial cancers [15]. The pathogenesis and development of ovarian cancer have also been closely linked to inflammatory processes with various proinflammatory cytokines to stimulate CRP production [16, 14]. In a multicentric study, preoperative serum CRP was evaluated in 623 patients with EOC. Serum CRP was significantly associated with the International Federation of Gynecologists and Obstetricians stage and postoperative residual tumour mass, but not with histologic grade and type [14]. In a retrospective single-centre study, Hefler-Frischmuth *et al.* observed that the serum CRP significantly correlated with FIGO Stage, residual tumour mass, and patient age, but not with tumour grade and histologic type in the subgroup of patients with EOC *vs.* ovarian tumours of low malignant potential *vs.* benign ovarian tumours [17]. Xavier *et al.* [18] reported differences in the CRP values, depending on the stage of the menstrual cycle (slightly lower values in the early and late secretory stage) in the blood of endometrial patients, as compared to the control group. Having considered these findings, the present authors determined the CRP level in the blood serum of women with endometrial cysts, and of patients with endometrial cysts and coexistent grade III peritoneal endometriosis, but no statistically significant changes between these two groups were noted [18]. No statistically significant differences in the CRP levels were observed among patients whose ovarian lesions included endometrial cysts with no coexistent peritoneal endometriosis or mature teratomas [19]. In turn, Ose *et al.* [15] in a nested case-control cohort study in the European Prospective Investigation into Cancer and Nutrition (EPIC) to evaluate CRP and EOC risk by tumour characteristics suggested that high CRP is associated with increased risk of overall EOC. Furthermore, hs-CRP concentration in patients with benign and malignant breast disease is completely different [20]. Ovarian tumours, irrespective of the lesion character, can rotate around the fallopian tube. Bakacak *et al.* [21] observed that the measurement of hs-CRP in a rat model seems to form a valuable plasma marker in early detection and diagnosis of ovarian torsion.

In recent years, literature sources have underlined the significance of fibrinogen and CRP in diagnosing malignant cancerous ovarian tumours. Therefore, this study aimed to assess blood coagulation, along with CRP and hs-CRP levels in the blood serum of patients suffering from ovarian lesions. Unfortunately, the authors failed to observe similar correlations, which they believe might have resulted from an insufficient cohort size.

Conclusion

Statistically significant differences were found in the fibrynogen and d-dimer profiles among patients with benign and malignant ovarian tumours. However, this requires further investigations on larger patient groups.

Acknowledgement

The study was financed with the funds for education as a research project 502-01-0111-01-38-03594 entitled: "Study of specific chemokines and non-chemokine factors and apoptotic proteins affecting the occurrence of benign neoplasms of the female reproductive tract: endometrial cysts, mature teratomas, uterine sarcoma and minor pelvic pain".

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