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ORIGINAL ARTICLE

Do inflammatory factors play a significant role in etiopathogenesis of endometrial cysts? Part 1

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Abstract

Endometriosis is an estrogen-related chronic condition which consists in the implantation and growth of endometrial cells outside the uterine cavity. It has an immune and inflammatory background, and to-date the precise etiopathogenesis of endometrial cysts has not been unequivocally defined. The objective of the study was evaluation of the indicators of the inflammatory state, including RANTES and the levels of C-reactive protein, leukocytes, fibrinogen and iron in the blood serum of patients with endometrial cysts (n=48) and benign ovarian tumours of mature teratoma type (n=38). Statistical analysis was performed using the Mann-Whitney Rank Sum Test. The p values $p<0.05$ were considered statistically significant.

Results: While comparing the results, respectively in groups, the mean levels in blood serum were as follows: RANTES 31,429.79 pg/ml (from 26,576.6 – 99,605.00) vs. 26,988.72 pg/ml (from 26,013.58 – 113,435.00) for p=0.428; CRP and WBC 2.13 vs. 1.54 mg/l; p=0.076 and 5.35 vs. 6.7; p=0.029; fibrinogen 3.12 vs. 2.57 mg%; $p<0.001$); iron level 87.20 vs. 78.01 ug/dl for p=0.430, and CA-125 36.50 vs. 15.08 U/ml; $p<0.001$).

Conclusions: Statistically significant differences were observed in the levels of WBC, fibrynogen and CA-125 in blood serum. Therefore, the role of the inflammatory factor in the etiopathogenesis of endometrial cysts still remains unexplained, and the presented study may emerge as pioneer investigations in the area of etiology of endometriosis.

Key words

endometriosis, endometrial cysts, benign ovarian tumours, mature teratoma, RANTES

INTRODUCTION

Endometriosis is an estrogen-related chronic condition which consists in the implantation and growth of endometrial cells outside the uterine cavity on the immune and inflammatory background [1, 2]. The disease occurs mainly in the form endometrial cysts (in 17–44% of patients at reproductive age) which, with respect to the dark brown liquid contents, are commonly described as chocolate cysts, as well as in the form of peritoneal implants and adhesions [3, 4, 5]. To-date, the precise etiopathogenesis of endometrial cysts has not been unequivocally explained. It is commonly considered that they develop as a result of reflux and adhesion of the fragments of ovarian epithelium, invagination of the cortex and cystic hyperplasia. Due to the conducive hormonal environment, the ovary is more susceptible to implantation and growth of the endometrium. Endometrial cells, while penetrating deeper into the stroma, may form single or multiple cysts, often of a large size, filled with dark, stale, sludgy-brown blood and exfoliated cells [6]. Elevated levels of cytokines described in many scientific reports may evidence the ongoing local endometriosis of an inflammatory character [7, 8, 9]. However, their effect is usually limited to the site of action, because their production is transitory (in response to a stimulus) by locally activated cells. The levels of these substances, including interleukin (IL)-4, IL-6, IL-8, IL-10 and RANTES (Regulated upon Activation, Normal T cell Expressed and Secreted) frequently correlates with the degree of clinical advancement of endometriosis, among other things, the IL-8 level is elevated in advanced stages of the disease, and the IL-6 level is considerably higher in the case of endometrial ovarian cysts [8, 10, 11]. In addition, in the blood of patients with endometriosis, higher levels of C-reactive protein (CRP) and many other inflammatory cytokines are observed [12]. Also, the disrupted pro-oxidant – anti-oxidant balance within the peritoneal cavity may play some role in the development of endometriosis. An increased level of oxygenated cholesterol LDL was noted in the peritoneal fluid of women with advanced stages of endometriosis [13, 14]. Irrespective of the above-mentioned theories, changes in the immune system enable the implantation and growth of the fragments of endometrium at ectopic sites, and the problem of the etiology of endometrial cysts seems to be still omitted by many researchers. In generally available medical databases there is no unequivocal answer to this question.

The objective of the presented study was a comparative evaluation of the indicators of the inflammatory state, including RANTES, the levels of C-reactive protein, white blood cells, fibrinogen and iron in the blood serum of patients with endometrial cysts and benign ovarian tumours of the mature teratoma type.

METHOD AND MATERIALS

The study group were patients (n=86) who received laparoscopic treatment in the Department of Mother and Child Health and Clinic of Surgical Gynaecology, University of Medical Sciences in Poznań, due to changes concerning the uterine appendages. The criteria for inclusion in the study were: normal obstetric history, good state of health

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with no concomitant diseases, intraoperative diagnosis of endometrial cyst and/or benign ovarian tumour of the mature teratoma type, without concomitant micro- and macroscopic peritoneal endometriosis (during laparotomy the change was excised and the peritoneum specimen collected and subjected to intraoperative histopathological assessment). Before the surgery no abnormalities were observed in the thrombocytic system of patients.

Blood for tests was collected on admission to hospital, i.e. the day before surgery. Some of the tests were performed immediately in the hospital laboratory (the tests also included determination of: C-reactive protein, iron, fibrinogen, whole blood count and CA-125 marker level). Blood for the remaining tests was centrifuged and frozen at the temperature of -20 °C.

After histopathologic verification the patients were divided into two groups. Group E were women (n=48) with histopathologically diagnosed endometrial cysts, without concomitant foci of peritoneal endometriosis, and Group T (n=38), control, were patients who had undergone laparoscopic treatment of benign ovarian tumours of the mature teratoma type. Statistical analysis of the results obtained was performed using the Mann-Whitney Rank Sum Test. The p values p<0.05 were considered statistically significant.

RESULTS

Group E (endometrial cysts) covered 48 women aged 30±4.61, median (Me) 31, who had body weight and height: 66.98±13.13 (Me=64) kg and 170.72±7.00 (Me=170) cm, respectively. Menarche occurred at the age of 13.75±0.99 (Me =14), regular menstruation 28.36±2.03 (Me=28) days, and menstruation duration 5.64±1.29 (Me=6) days. Unilateral cysts were located on the left side (n=23), of the size 48.13±17.87 mm, while on the right side in 25 women, diameter 49.29±14.91 mm.

Group T (mature teratomas) covered 38 women aged 27.03±4.52, (Me) 26, who had body weight and height: 64.70±11.83 (Me=64) kg and 170.46±6.07 (Me=172) cm, respectively. The first menstrual period occurred at the age of 13.89±1.58 (Me =14), regular, every 28.62±1.67 (Me=28) days and duration 4.97±1.36 (Me=5) days. Unilateral cysts were located on the left side (n=13), size 44.29±10.92 mm, and on the right side in 25 women, diameter 48.64 ±15.03 mm.

The selected groups of women with changes concerning the uterine appendages in the form of endometrial cysts vs. mature teratomas were relatively uniform with respect to age (31 vs. 26; p=0.002), body weight (64 vs. 64 kg; p=0.394), height (170 vs. 172 cm; p=0.421), duration of menstrual cycle (28 vs. 28 days; p=0.082) and duration of menstrual period (6 vs. 5 days; p=0.021). Tables 1 and 2 present the levels of RANTES, CA-125 and C reactive protein, as well as whole blood count, fibrinogen and iron in both groups.

Table 1. Levels of RANTES, CA 125 and CRP in blood serum of patients with changes in appendages in the form of endometrial cysts (Group E) and mature teratomas (Group T).

Determinations	Group	Mean		Max	Min	Median	P
RANTES [pg/ml]	**Group E**	31,429.79	26,576.6	99,605.00	12.1	24,886.00	.428
	Group T	26,988.72	26,013.58	113,435.00	32.6	17,941.5	
CA 125 [U/ml]	**Group E**	49.69	33.77	171.90	8.71	36.50	.001*
	Group T	22.82	21.49	128.30	10.00	15.08	
CRP [mg/l]	**Group E**	2.95	4.10	27.06	0.05	2.13	.076
	Group T	1.72	0.85	3.38	0.29	1.54	

* p values p<0.05 were considered statistically significant, Mann-Whitney Rank Sum Test.

Table 2. Levels of other agents in blood serum of patients with changes in appendages in the form of endometrial cysts (Group E) and mature teratomas (Group T).

Determinations	Group	Mean	±SD	Max	Min	Median	P
HGB [mmol/l]	**Group E**	8.07	0.70	9.84	6.35	8.02	.103
	Group T	8.32	1.20	12.50	5.27	8.40	
RBC [T/l]	**Group E**	4.65	0.91	285.10	3.91	4.62	.642
	Group T	4.68	0.37	5.53	3.86	4.74	
WBC [G/l]	**Group E**	6.08	2.25	12.52	3.49	5.35	.029*
	Group T	6.63	1.63	11.2	4.32	6.7	
HCT	**Group E**	34.77	13.56	46	0.37	38.9	.549
	Group T	34.91	14.47	49.9	0.389	39.7	
PLT [G/l]	**Group E**	264.88	38.44	351.20	163.00	267.80	.296
	Group T	254.22	51.65	357.00	163.00	258.90	
Fibrinogen [mg%]	**Group E**	3.26	0.45	3.98	2.60	3.12	.001*
	Group T	2.75	0.70	4.40	1.40	2.57	
Iron [ug/dl]	**Group E**	87.20	36.47	207.90	28.10	84.00	.430
	Group T	78.01	19.05	108.00	43.40	78.00	

* p values p<0.05 were considered statistically significant, Mann-Whitney Rank Sum Test.

DISCUSSION

Endometriosis affects approximately 10–15% women at reproductive age, and occurs in 20–50% of patients treated due to infertility, in as many as 70% of those suffering from chronic pain located in the lesser pelvis, pain related with menstrual cycle (60–80%), and with painful sex (in 25–50%) [9]. Ovarian endometriosis and endometrial cysts occur slightly more frequently on the left side of the lesser pelvis, and their asymmetric arrangement most probably results from the anatomical conditions, because the presence of the sigmoid colon in this region disturbs and slows down the flow of peritoneal liquid through the left part of the pelvis [15].

The controversy concerns the causes of the development of endometrial cysts. It is not known whether the development of cysts is the effect of the reflux flow and implantation of the exfoliated endometrium, or the result of metaplasia or a gradual penetration of surface implants and abnormal immune response. The walls of the cyst are usually relatively well separated from the ovarian stroma, although in the case of 'old' cysts and infiltrating forms of endometriosis there may develop fibrous-cicatrical changes and destruction of the entire ovary. The change is richly vascularized and may strongly branch into other regions of the ovarian cortex. In the course of time, the structure of the cyst changes: its wall becomes thicker, less vascularized, the amount of collagen fibres and macrophages filled with hemosiderin,

an iron-containing pigment, increases as a result of previous recurrent bleeding [6]. Thus, the question arises whether an excessive production of inflammatory agents is responsible for the development of endometrial cysts?

RANTES is a chemokine which stimulates T CD4+ lymphocytes chemotaxy and adhesion, especially activated lymphocytes which display the phenotype of memory cells, as well as virgin CD8+ lymphocytes. It reported that concentrations of RANTES are elevated in the peritoneal cavity of women with endometriosis and correlate with the severity of the disease [10]. Unfortunately, to-date, there have not been any studies comparing the concentration of RANTES in blood serum of patients with endometrial cysts without concomitant peritoneal endometriosis. Other studies may only be quoted in which inflammatory agents were determined. Fasciani et al. [11] compared the concentrations of vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8) in follicular cysts and ovarian endometriomata. The results of the study confirmed that VEGF levels detected in the ovarian endometriomata (1,140.0 ± 307.2 pg/ml) were significantly higher than those in the follicular cysts (189.9 ± 90.7 pg/ml) (p<0.001). IL-8 levels detected in the ovarian endometriomata (1,521.0 ± 180.1 pg/ml) were significantly higher than those observed in the follicular cysts (27.2 ± 12.4 pg/ml) (p<0.001) [11]. In the presented study, RANTES level was 31,429.79 pg/ml, on average (from 26,576.6 – 99,605.00), and was significantly higher than that obtained in the control group – 26,988.72 pg/ml (from 26,013.58 – 113,435.00) for p=0.428. However, no statistically significant differences were observed in serum RANTES levels in patients with endometrial cysts and mature ovarian teratoma.

C-reactive protein, lymphocytes (WBC), and fibrinogen determined in medical practice are acute phase proteins, and their levels increase, among others, in the case of chronic inflammatory processes. Xavier et al. [16] compared the levels of CRP in the blood of patients with endometriosis (n=25) and in a control group (n=13), according to the phase of menstrual cycle. In Phase I of the cycle, in the early and late proliferative phases, the mean values for C-reactive protein in patients with endometriosis and in the control group were: 2.29 vs. 0.68mg/l and 1.10 vs. 0.59mg/l, respectively. The values of CRP were slightly lower in the early and late secretion stage (Phase II of the cycle) and were: 1.09 vs. 0.90mg/l and 0.60 vs. 0.87mg/l [16], respectively. It is interesting that in a multicentre study of 623 patients with epithelial ovarian cancer, preoperative serum CRP was evaluated (3.6 mg/dL) and was significantly associated with the International Federation of Gynaecologists and Obstetricians stage (p<0.001) and postoperative residual tumour mass (p<0.001), but not with the histologic grade (p=0.1) and type (p=0.7) [17]. In turn, in a retrospective single-centre study, serum CRP was evaluated in 576 patients with benign tumours and in 44 patients with ovarian tumours of low malignant potential, and n=198 epithelial ovarian cancer. Median (25th–75th percentiles) serum CRP levels in patients were 0.5 (0.5–0.6) mg/dL, 0.5 (0.5–0.9) mg/dL and 1.36 (0.5–4.9)mg/dL, respectively (p<0.001) [18]. In our preliminary study conducted in 2008 in a group of women with endometrial cysts (n=10), the level of C-reactive protein was 1.22 mg/l, on average, and the level of WBC – 8.92 G/l, while in the group of patients with endometrial cysts with concomitant peritoneal endometriosis grade 3 – 2.07 mg/l and WBC 6.93 G/l [19]. While comparing the CRP and WBC levels in the blood serum of patients with endometrial cysts vs. mature teratomas (2.13 vs. 1.54 mg/l; p=0.076 and 5.35 vs. 6.7; p=0.029), no statistically significant differences in CRP values were observed between the groups examined. Slightly larger differences in CRP values noted in the presented study may result from the larger size of the study group and the unification of the groups. Fibrinogen, apart from its function as an acute phase protein, also participates in the coagulation system processes, and the values from 2 – 4 g/l are adopted as a physiological fibrogen concentration in blood. Grabowski et al. [20] analyzed blood clotting parameters in patients who had undergone surgery due to endometrial cysts, compared to a control group with benign tumours of the uterine appendages. In patients suffering from endometriosis, slightly higher mean concentrations of plasminogen (p>0.05) and α2-antyplasmin levels (p>0.05) were found, and lower concentration of plasminogen-1 activator inhibitor (p>0.05), as well as lower activity of tissue plasminogen activator in blood serum (p>0.05), compared to the control group. The researchers suggest that the described changes within the fibrinolytic system often seem to be contradictory. This indicates that the mechanism for the development of foci and formation of adhesions in the course of the disease is complex and remains unexplained. This, however, does not exclude their presence on a local level, at the site of the endometriosis and in its vicinity [20]. In our preliminary study conducted in 2008 in a group of women with endometrial cysts (n=10), the mean concentration of fibrinogen in blood serum was 3.22 mg/l, whereas in the group of patients with endometrial cysts with concomitant peritoneal endometriosis grade 3 – 3.04 mg/l [5]. The statistically significant differences between the examined groups (cysts vs. teratomas) – 3.12 vs. 2.57 mg%, respectively; (p<0.001), seem even more interesting.

Iron in the organism is mainly a component of haemoglobin and hemosiderin, and the mean values are approximately 10 μg/dl. The level of iron in blood serum shows certain daily fluctuations during the menstrual cycle, and the decrease in its level accompanies anaemia, as well as acute and chronic infections and inflammatory reactions. In our 2008 preliminary study, statistically significant differences in iron values were found between patients with endometrial cysts (101.18 ug/dl, on average), and in blood serum of patients with endometrial cysts with concomitant peritoneal endometriosis grade 3 of advancement (55.45 ug/dl, on average; p<0.001) [19]. While comparing the level of iron between patients treated due to endometrial cysts, and those who received treatment due to teratomas, no statistically significant differences were observed, the mean levels were 87.20 vs. 78.01 ug/dl, which were close to those obtained in the pilot study. The objective of the study by Polak et al. [21] was evaluation of the level of iron in the peritoneal fluid in women with endometriosis (25 patients with endometriosis grade 1 and 2, and 25 women with grade 3 and 4 of the disease, while the control group were 25 patients who had undergone surgery due to serous ovarian cysts). The concentration of the above-mentioned element was statistically significant (p<0.01), and it was higher in the peritoneal fluid of women with endometriosis (123–504μg/dl), compared to the control group (63–196μg/dl). The researchers also found that the level of iron in the peritoneal fluid of women with grade 3 and 4 of advancement (211–504μg/dl), was significantly higher statistically (p<0.01), compared to patients with grades 1

and 2 of the advancement of the disease (213–311μg/dl). Thus, a disrupted iron metabolism in the peritoneal fluid of women with endometriosis suggests the participation of this element in the pathogenesis of endometriosis. In addition, an increased concentration of iron ions in the peritoneal fluid correlates with the degree of advancement of the disease [21]. Iizuka et al. [22] investigated the level of iron in the biopsy fluid collected in benign tumours of the appendages. The highest iron concentration was obtained in fluid collected from the corpus haemorrhagic (1.957.5 μmol/l) and from the endometrial cyst (1.749.6 ± 41.5 μmol/l), while the lowest – from the luteal ovarian cyst (1,393.8 μmol/l) [22]. Similarly, Yamaguchi et al. [23] evaluated fluid from 21 endometrial and 11 non-endometrial cysts, and the average concentration of free iron was significantly higher in the group of endometrial cysts (100.9 vs. 0.075 mmol/L; $p<0.01$) [23]. Unfortunately, in the above-mentioned studies the circulating iron levels were not determined.

The problem of serum markers in endometriosis and in the diagnostics of endometrial cysts still evokes great interest. From among numerous biochemical markers (CA-125, CA 19–9, CA-15–3 and IL-6, TNF-α), only CA-125 protein proved to be useful in every day clinical practice [3]. Unfortunately, this marker is characterised by a low sensitivity of 28% and a large dispersion of sensitivity – 24–94%, whereas the specificity is high – 83–93% [24, 3]. Nevertheless, it should be kept in mind that elevated CA-125 values (the scope of normal value up to 35 U/ml) do not accompany exclusively endometrial cysts and deep infiltrating endometriosis [3]. In the case of endometriosis, it seems that the level of CA-125 may be the marker of the effectiveness of surgical treatment (pre-operative values between 16 – 25 U/ml, and post-operative values lower than 16 U/ml, which correlates with a larger number of pregnancies 12 months after the surgery [25]. The investigations carried out by Szubert et al. [26] show that the mean value of CA-125 serum concentration in the endometriosis group (pelvic endometriosis stages 2–4 or ovarian cysts, n=44) was 33.98 U/ml vs. 9.3 U/ml in the control group (without endometriosis, n=15). The mean value of CA-125 in peritoneal fluid was 1,241.88 U/ml in the non-endometriosis group, compared to 2,640.23 U/ml in the study group; both results were statistically significant ($p<0.05$). A significant correlation was found between the stage of endometriosis and CA-125 serum concentration ($R = 0.5993$;$p<0.001$) [26]. Similar results were obtained in the presented study (cysts vs. teratomas: 36.50 vs. 15.08 U/ml; $p<0.001$), which shows that the normal values of CA-125 do not exclude the possibility of the occurrence of endometrial cysts).

Irrespective of the above-mentioned theories, changes in the immune system enable the implantation and growth of the fragments of endometrium in the ectopic site, and the problem of etiology of the endometrial cysts seems to be still omitted by many researchers. Due to scarce literature reports, the presented study may emerge as a pioneer investigation in the area of the etiology of endometriosis, and the authors believe it will be a valuable expansion of knowledge concerning endometriosis.

CONCLUSIONS

Statistically significant differences were observed in the levels of WBC, fibrynogen and CA-125 in blood serum. No statistical differences were observed in the levels of RANTES, iron and CRP in blood serum. Therefore, the role of the inflammatory agent in the pathogenesis of endometrial cysts still remains unexplained.

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