The role of chemokine and non-chemokine factors in pain-related complaints in patients with endometrial cysts

Udział czynników chemokinowych i niechemokinowych w występowaniu dolegliwości bólowych u pacjentek z torbielami endometrialnymi

Karolina Chmaj-Wierzchowska[1], Małgorzata Kampioni[2,3], Maciej Wilczak[3], Stefan Sajdak[2], Tomasz Opala[1]

[1] Department of Mother's and Child's Health, University of Medical Sciences, Poznan, Poland
[2] Clinic of Surgical Gynecology, University of Medical Sciences, Poznan, Poland
[3] Department of Medical Education, University of Medical Sciences, Poznan, Poland

Abstract

Objectives: *Endometriosis is a chronic disease manifested as peritoneal endometrial implants and adhesions, as well as endometrial cysts, with pain as the dominant component.*

The aim: *The aim of the study was to evaluate the role of chemokine (MCP-1, MCP-2, MIP-1 , MIP-1 and RANTES) and non-chemokine (urocortin, ghrelin, and leptin) factors in the intensity of pelvic pain in women with endometrial cysts.*

Material and methods: *A total of 86 women, aged 18-38, treated laparoscopically between September 2009 and November 2012, due to adnexal changes, i.e. endometrial cysts and mature teratomas, were recruited for the study. On a numeric rating scale, i.e. PSS (Pain Sensation Scale – according to Johnson), the patients rated pain intensity. The level of pain-related stress was investigated with the Pain Distress Scale (PDS, according to Johnson).*

Results: *Medians for MCP-1, MCP-2, MIP-1 , MIP-1 and RANTES concentrations were not statistically significantly different. The respondents rated pain intensity during menses as 6 and 3 points in the E and T groups, respectively (6 vs. 3 points; p=0.001). Statistically significant differences were also observed for pain intensity during work (apart from menses), (2 vs. 2 points, p=0,014) and during sexual intercourse (apart from menses) (3 vs. 1 points, p=0.006). Pain-related stress levels were higher in the T group as compared to the E group (3 vs. 5 points; p=0.007).*

Conclusions: *It seems safe to conclude that chemokines and leptin may play a significant role in the occurrence of pain complaints among women with endometrial cysts. Further research might result in implementation of new treatment methods for pain management, especially in terms of pharmacotherapy.*

Key words: **MCP-1** / **MCP-2** / **MIP-1α** / **MIP-1β i RANTES** / **pain** / **endometriomas** /

Streszczenie

Wstęp: *Endometrioza jest przewlekłą chorobą, występująca pod postacią wszczepów i zrostów otrzewnowych jak również torbieli endometrialnych w przebiegu, której dominuje komponenta bólowa.*

Cel pracy: *Celem pracy była ocena wpływu chemokin (MCP-1, MCP-2, MIP-1 , MIP-1 i RANTES) i czynników niechemokinowych (urokortyny, greliny i leptyny) na występowanie dolegliwości bólów miednicy mniejszej u kobiet z torbielami endometrialnymi.*

Corresponding author:
Karolina Chmaj-Wierzchowska,
Department of Mother's and Child's Health, University of Medical Sciences, Poznan
Poland, 60-535 Poznań, ul. Polna 33
tel./fax: +48 61 841 92 73
e-mail: karolinachmaj@poczta.onet.pl

Otrzymano: **27.04.2014**
Zaakceptowano do druku: **17.07.2014**

Materiał i metody: *Badaniem objęto łącznie 86 kobiet, w wieku 18-38 lat, leczonych laparoskopowo, z powodu zmian w przydatkach o charakterze torbieli endometrialnych i potworniaków dojrzałych, od września 2009 r. do listopada 2012 roku. Na skali intensywności bólu numerycznej (Pain Sensation Scale – PSS, wg. Johnsona) pacjentki zaznaczały odpowiedzi na pytania dotyczące stopnia nasilenia bólu. Badano również poziom stresu (Pain Distress Scale – PDS, wg. Johnsona) jaki występuje podczas dolegliwości bólowych.*

Wyniki: *Mediany MCP-1, MCP-2, MIP-1 , MIP-1 i RANTES, urokortyny, leptyny, greliny nie różniły się istotnie statystycznie. Według respondentek, mediana natężenia bólu, występującego podczas miesiączki, wynosiła 6 pkt. w grupie kobiet z torbielami endometrialnymi a u pacjentek z potworniakami 3 pkt. (6 vs 3; p=0,001). Różnice istotne statystycznie występowały także dla wartości odpowiadającym natężeniu dolegliwości bólowych, poza miesiączką, w pracy zawodowej (2 vs 2pkt., p=0,014) i w trakcie odbywania stosunków płciowych (3 vs 1 pkt., p=0,006). Stopień odczuwania stresu z powodu dolegliwości bólowych był wyższy w grupie pacjentek z potworniakami vs torbielami (3 vs 5; p=0,007).*

Wnioski: *Chemokiny oraz leptyna mogą mieć znaczący wpływ na występowanie dolegliwości bólowych u pacjentek z torbielami endometrialnymi. Dalsze badania w tym obszarze mogłyby przyczynić się zastosowania nowych metod leczenia bólu, zwłaszcza w zakresie farmakoterapii.*

Słowa kluczowe: **MCP-1** / **MCP-2** / **MIP-1α** / **MIP-1β i RANTES** / **ból** / / **torbiel endometrialna** /

Introduction

Endometriosis is a chronic disease manifested as peritoneal endometrial implants and adhesions, as well as endometrial cysts, with pain as the dominant component [1, 2]. Chronic pain, cyclic and typically intensifying during menstruation, is the main symptom of endometriosis. The intensity of pain often does not correlate with disease advancement and the size of ovarian lesions as both, highly intense pain accompanying small, surface peritoneal lesions as well as absence of pain in case of large ovarian cysts have been observed [3].

The aim of the study was to evaluate the role of chemokine (MCP-1, MCP-2, MIP-1α, MIP-1β and RANTES) and non-chemokine (urocortin, ghrelin, and leptin) factors in the intensity of pelvic pain in women with endometrial cysts.

Material and methods

A total of 86 women, aged 18-38, treated laparoscopically between September 2009 and November 2012 at the Obstetrics and Gynecology Hospital, PUMS, due to adnexal changes, i.e. endometrial cysts and mature teratomas, were recruited for the study. The inclusion criteria were: no history of obstetric complications, good overall condition without concomitant diseases, surgical diagnosis of endometrial cysts without accompanying macroscopic peritoneal endometriosis and/or ovarian tumor in the form of mature teratomas (i.e. hormone-independent lesions) to avoid the influence of estradiol on serum chemokine levels. Pre-operative coagulation tests revealed no clotting abnormality. All patients underwent diagnostic laparoscopy in the follicular phase of the menstrual cycle. None of the patients had undergone infertility treatment.

The histopathologic test was the basis for qualifying women into the group with endometrial cysts or benign tumors in the form of mature teratomas. After surgical verification, the patients were subdivided into two study groups. The E (endometrial cysts) group was comprised of women (n=48, aged 30±4.61 years, median (Me) 31 years) with histopathologically confirmed endometrial cysts, without accompanying endometrial foci in the peritoneal cavity. The T (mature teratomas) group included subjects (n=38, aged 27.03±4.52 years, Me=26 years) after laparoscopic treatment for ovarian benign tumors in the form of mature teratomas.

Fasting blood samples were drawn upon admission, i.e. one day pre-operatively, in the morning. Blood for MCP-1, MCP-2, MIP-1α, MIP-1β and RANTES assays, as well as for urocortin, ghrelin, and leptin, was centrifuged and frozen at -20ºC. The levels of CCL2/MCP-1 (R&D, USA), CCL8/MCP-2 (R&D, USA), MIP-1α (USCN, China), MIP-1β (USCN, China) and CCL5/RANTES (R&D, USA), as well as urocortin (USCN, China), ghrelin (Millipore, USA) and leptin (Millipore, USA), were obtained with ELISA, and repeated twice to avoid measurement error. The concentration values (pg/ml) were given as mean±SD (standard deviation) and median (Me).

The questionnaire, designed especially for the study, included questions about socioeconomic data, menstrual and obstetric history, concomitant diseases, history of surgical (including gynecologic) interventions, and pain complaints. On a numeric rating scale, i.e. PSS (Pain Sensation Scale – according to Johnson) [160], the patients rated pain intensity during the following: menstruation, everyday life activities (apart from menses), work (apart from menses), sexual intercourse (apart from menses), and defecation (apart from menses) – with 0 for 'no pain' and 10 for 'worst pain'. The level of pain-related stress was investigated with the Pain Distress Scale (PDS, according to Johnson), with 0 for 'no stress' and 10 for 'worst stress' [160].

The quantitative data were presented as mean and standard deviation (SD), with additionally calculated medians (Me), minimum (Min) and maximum (Max) values. The significance of the differences for parameters of non-normal distribution or non-homogeneous variance for two groups of variables was tested with non-parametric U Mann-Whitney test, i.e. for the levels of MCP-1, MCP-2, MIP-1α, MIP-1β and RANTES, urocortin, leptin and ghrelin. The qualitative data from the questionnaire on the characteristics of the investigated population were presented as the number of individuals in a given category (n) and percent

share in the group (%).The chi-square test of independence was used to compare qualitative data between the groups, i.e. marital status, education, place of inhabitance, smoking, professional activity, parity, and the number of miscarriages. Non-parametric Mann-Whitney test was used for the statistical analysis of the general characteristics of patients with endometrial cysts and mature teratomas, taking into consideration their age, BMI, height, and the diameter of adnexal lesions. Spearman's rank correlation coefficient was used to evaluate correlations between variables and their strength, if at least one parameter had non-normal distribution. Pain intensity was assessed with the use of a questionnaire with a scale for evaluating pain (numeric scale) and accompanying stress (pain-related stress scale). The Mann-Whitney test was used for statistical analysis of the obtained results, whereas the correlation was tested with Spearman correlation coefficient. The value of $p \leq 0.05$ was considered as statistically significant. Statistical analyses were performed with STATISTICA, StatSoft.

The Local Ethics Committee (PUMS) approved of the study (8 January, 2009, no. 10/2009). The funding for the study was obtained from research funds between 2009-2013 (research project NN404 195037).

Results

The age of the investigated women with adnexal masses (endometrial cysts vs. mature teratomas) was statistically significantly different (31 vs. 26 years, respectively; p=0.002). No statistically significant differences were found with regard to BMI, length of the menstrual cycle, duration of the menstruation, or the size of the ovarian lesions.

The general characteristics of the patients are presented in Tables I and II.

Analysis of laboratory assays

Levels of urocortin, leptin, and ghrelin in groups E and T were analyzed. Their medians were 105.31 vs. 120.84 pg/ml for urocortin, 7.16 vs. 9.13 pg/ml for leptin, and 584.33 vs. 657.82 pg/ml for ghrelin, respectively. The values were not statistically significantly different (Table 3). Medians for MCP-1, MCP-2, MIP-1α, MIP-1β and RANTES concentrations were not statistically significantly different (Table IV).

Pain analysis

The respondents rated pain intensity during menses as 6 and 3 points in the E and T groups, respectively (6 vs. 3 points; p=0.001). Statistically significant differences were also observed for pain intensity during work (apart from menses), (2 vs. 2 points, p=0,014) and during sexual intercourse (apart from menses) (3 vs. 1 points, p=0.006). Pain-related stress levels were higher in the T group as compared to the E group (3 vs. 5 points; p=0.007). The analysis of visual evaluation of pain intensity and the related stress is presented in Table V.

Spearman correlation test of laboratory findings was performed in the E group (Table VI) and the T group (Table VII) for further analysis of pain intensity. Positive, statistically significant correlation was observed between MIP-1α and pain during defecation (apart from menses) (r=0.464; p=0.0131) and MCP-2 and pain during work (apart from menses) (r=0.359; p=0.0437). A negative correlation was found between leptin concentrations and stress levels (-0.387; p=0.00744) in patients with endometrial cysts. Blood serum analysis revealed a negative, statistically significant correlation between ghrelin and pain during menstruation (r= -0.608; p=0.00132) in patients with mature teratomas.

Discussion

Endometriosis affects approximately 10–15% women at reproductive age, 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%). Endometriosis, despite its chronicity, need not necessarily deteriorate the quality of patient life. Evaluation of pain intensity remains an essential element of pain management in the affected individuals [4]. Chemokines are small proteins with a wide range of biological activities and specific chemoattractant function [5, 6].

High concentrations of the MCP-1 chemokine in the peritoneal fluid have been observed in women with endometriosis and these values correlated with disease advancement [7]. Drosdzol-Cop A et al. [8], investigated MCP-1 levels in blood serum and the peritoneal fluid as a marker of the chronic pelvic pain (CPP) syndrome in young girls (n=50), aged 13-19 years. They found that MCP-1 concentrations were not statistically significantly different in patients with diagnosed endometriosis as compared to healthy controls, without foci of endometriosis confirmed laparoscopically [8].

In our study, blood serum MCP-1 levels were not statistically significantly different and did not correlate with pain intensity in both groups. The comparison of blood serum MCP-2 levels revealed median values to be 282.72 (2335.89) pg/ml vs. 346.87 (262.69) pg/ml in the E and T groups, respectively.

Table I. General characteristics for endometrial cysts (E) and mature teratomas (T) groups.

	E group	T group	p
	mean±SD (median)		
age [years]	30.00±4.60 (31)	27.03±4.52 (26)	0.002*
BMI [kg/m2]	23.00±13.00 (23)	22.70±12.00 (22)	0.396
length of the menstrual cycle [days]	28±6.00 (28)	28±7.00 (28)	0.082
duration of the menstruation	6±2.00 (6)	5±3.00 (5)	0.021
lesion diameter in the right ovary [mm]	49.29±14.91	48.64±15.03	0.876
lesion diameter in the left ovary [mm]	48.13±17.87	44.29±10.92	0.474

*statistical significance level for Mann-Whitney test

Table II. Patient characteristics for endometrial cysts (E) and mature teratomas (T) groups.

		E group n=48 (100%)	T group n=38 (100%)	p
marital status	- single	26 (54.2)	14 (36.8)	0.153
	- married	19 (39.6)	22 (58.0)	
	- divorced	3 (6.2)	1 (2.6)	
	- widow	0	1 (2.6)	
education	-primary	2 (4.2)	5 (13.2)	<0.001*
	- VET	3 (6.2)	3 (7.9)	
	- secondary	29 (60.4)	2 (5.3)	
	- higher (B.A.)	3 (6.2)	8 (21.0)	
	- higher (M.A.)	11 (23.0)	20 (52.6)	
place of inhabitance [population]	< 5 000	31 (64.6)	18 (47.4)	0.133
	- 5 001 – 50 000	7 (14.6)	5 (13.2)	
	- 50 001 – 100 000	3 (6.2)	4 (10.5)	
	> 100 001	7 (14.6)	11 (28.9)	
smoking	- no	42 (87.5)	36 (94.7)	<0.001*
	- yes	6 (12.5)	2 (5.3)	
parity	- nullipara	34 (70.8)	20 (52.7)	0.074
	- primipara	5 (10.4)	11 (28.9)	
	- secundipara	9 (18.8)	7 (18.4)	
miscarriage	- no	46 (95.8)	34 (89.5)	0.082
	- yes	2 (4.2)	4 (10.5)	
overall health condition	- poor	1 (2)	0 (0)	0.119
	- rather good	9 (18.8)	11 (28.9)	
	- good	31 (64.6)	14 (36.9)	
	-very good	7 (14.6)	13 (34.2)	
gynecological check-up	- more than 1/year	28 (58.3)	14 (36.9)	0.027*
	- once a year	14 (29.2)	13 (34.2)	
	- once every 2 years	4 (8.3)	11 (28.9)	
	- seldom	2 (4.2)	0	

* statistical significance level for chi-square test

Table III. Comparison of urocortin, leptin, ghrelin levels in blood sera of women with endometrial cysts (E group) and mature teratomas (T group).

assays	group	mean	±SD	max.	min.	median	p
urocortin [pg/ml]	**E group**	252.37	348.77	1228.604	0.145	105.1	0.727
	T group	256.03	353.92	1227.27	1.03	120.84	
leptin [pg/ml]	**E group**	8.06	5.19	22.25	0.11	7.16	0.284
	T group	9.82	6.31	20.68	1.52	9.13	
ghrelin pg/ml]	**E group**	606.78	261.18	1892.06	180.00	584.33	0.153
	T group	627.42	158.50	884.58	185.67	657.82	

* statistical significance level for Mann-Whitney test

Analysis of the positive correlation between the MCP-2 levels and pain intensity during work (r=0.359; p=0.0437) in the group of women with endometrial cysts as compared to teratomas (r=0.0718; p=0.74), revealed that visual evaluation on a numeric rating scale of pain intensity during work was comparable and statistically significant (median 2 vs. 2; p=0.014). What is more, pain-related stress level is lower in women with endometriosis. Łuczak et al. [9], presented psychological profiles of patients with endometriosis and found that the majority of the affected women accept the disease, what allows them to avoid its negative influence on psychosocial functioning. Also, they have high level of self-efficacy, what signifies appreciation of one's own resourcefulness in a challenging and stressful situation [9].

Bedaiwy et al. [10], observed that elevated concentrations of leptin in the peritoneal fluid correlated with pelvic pain and advancement of endometriosis. Leptin level in the peritoneal fluid was statistically significantly higher in women treated for endometriosis as compared to patients with idiopathic infertility and controls [10]. Analysis of the statistically significant, negative correlation between leptin and stress levels (r= -0.387; p=0.00744) in the group of women with endometrial cysts, demonstrated that visual assessment of pain-related stress level revealed it to be was higher in women with teratomas as compared to endometrial cysts (p=0.007). Regardless, pain intensity was reported to be higher in patients with endometriosis, e.g. during menses (median 6 vs. 3; p=0.001), as well as during sexual intercourse

Table IV. Concentrations of MCP-1, MCP-2, MIP-1 , MIP-1 and RANTES in blood sera of women with endometrial cysts (E group) and mature teratomas (T group).

assays	group	mean	±SD	max.	min.	median	p
MCP-1 [pg/ml]	**E group**	124.19	84.01	506.34	38.88	87.17	0.598
	T group	128.32	76.10	290.4	52.2	91.92	
MCP-2 [pg/ml]	**E group**	282.72	216.00	1037.14	88.71	235.89	0.204
	T group	346.87	213.61	860.58	99.16	262.69	
MIP-1α [pg/ml]	**E group**	261.61	254.13	1621.78	66.86	185.73	0.483
	T group	412.95	488.46	2153.32	82.55	199.59	
MIP-1β [pg/ml]	**E group**	45.10	79.28	510.49	16.14	20.82	0.091
	T group	68.16	139.92	677.41	16.2	21.53	
RANTES [pg/ml]	**E group**	31 429.79	26 576.6	99 605.00	12.1	24 886.00	0.428
	T group	26 988.72	26 013.58	113 435.00	32.6	17 941.5	

* statistical significance level for Mann-Whitney test

Table V. Analysis of visual assessment of stress level (6), and pain intensity during the following (1-5):

	E group median	T group median	p
1. menses	6	3	0.001*
2. everyday tasks, apart from menses	2	1	0.672
3. work, apart from menses	2	2	0.014*
4. sexual intercourse, apart from menses	3	1	0.006*
5. defecation, apart from menses	2	1	0.128
6. pain-related stress	3	5	0.007*

* p<0.05 statistical significance level for Mann-Whitney test

Table VI. Evaluation of pain intensity and stress level in women with endometrial cysts.

	pain during menses	pain apart from menses during:				STRESS	p
		everyday tasks	work tasks	sexual intercourse	defecation		
MIP-1β [pg/ml]	0.128	0.0341	0.19	0.311	0.145	0.177	r
	0.4	0.84	0.272	0.106	0.395	0.239	p
MIP-1α [pg/ml]	0.0255	-0.267	0.24	**0.464**	0.109	0.102	r
	0.867	0.11	0.163	**0.0131***	0.525	0.497	p*
urocortin [pg/ml]	-0.0636	-0.0813	0.156	0.367	-0.141	0.2	r
	0.691	0.651	0.389	0.0642	0.431	0.203	p
RANTES [pg/ml]	0.082	0.000389	0.00911	-0.00698	0.125	-0.00385	r
	0.59	0.997	0.957	0.97	0.465	0.979	p
MCP-1 [pg/ml]	0.275	-0.0553	0.0668	0.0262	-0.0102	-0.00922	r
	0.0677	0.744	0.701	0.893	0.951	0.951	P
leptin [ng/ml]	-0.273	-0.0519	-0.126	-0.348	-0.00285	**-0.387**	r
	0.0664	0.755	0.46	0.0641	0.986	**0.00744***	p*
MCP-2 [pg/ml]	0.27	**0.359**	-0.17	-0.364	-0.0987	-0.0657	r
	0.0959	**0.0437***	0.359	0.073	0.589	0.685	p*
ghrelin [pg/ml]	0.181	0.0504	-0.221	-0.222	-0.0912	0.122	r
	0.289	0.793	0.256	0.306	0.63	0.47	p

* p<0.05 statistical significance level for Spearman correlation test

(apart from menses) (median 3 vs. 1; p=0.006). Interestingly, a positive correlation between MIP-1α and pain intensity during defecation (apart from menses) was found in patients with endometrial cysts (r=0.464; p=0.0131). In case of blood sera of women with teratomas, a negative correlation between ghrelin and menstruation-related pain was noted (r= - 0.608; p=0.00132). Numerous studies concerning endometriosis and pain have been reported. However, there is no consensus on the best method to evaluate pain in endometriosis and many scales have been used [11]. Changes in the immune system and the problem of etiology of the endometrial cysts seems to be still omitted by many researchers [12, 13, 14, 15]. Pain assessment remains a vital element of pain management in women with endometriosis but clinical data are scant.

Table VII. Evaluation of pain intensity and stress level in women with teratomas.

	Pain during menses	Pain unrelated to menses				STRESS	p
		in everyday life	at work	during intercourse	during defecation		
MIP1β [pg/ml]	-0.24	0.0511	-0.162	0.0696	-0.0066	-0.279	r
	0.178	0.787	0.407	0.707	0.972	0.115	p
MIP-1α [pg/ml]	-0.0153	0.094	-0.0153	0.167	0.124	-0.0349	r
	0.932	0.624	0.938	0.374	0.534	0.848	p
Urocortin [pg/ml]	0.0385	-0.211	-0.277	-0.268	-0.253	-0.123	r
	0.828	0.253	0.144	0.136	0.184	0.485	p
RANTES [pg/ml]	0.0689	-0.056	-0.011	-0.0852	-0.0519	-0.0477	r
	0.696	0.762	0.954	0.641	0.788	0.786	p
MCP-1 [pg/ml]	-0.191	-0.0288	-0.118	-0.0852	-0.159	-0.0801	r
	0.276	0.877	0.538	0.641	0.405	0.65	P
Leptin [ng/ml]	0.216	0.242	-0.208	0.237	0.169	-0.178	r
	0.218	0.189	0.276	0.189	0.376	0.312	p
MCP-2 [pg/ml]	-0.14	0.214	0.0718	0.17	0.175	0.234	r
	0.475	0.27	0.74	0.403	0.389	0.229	p
Ghrelin [pg/ml]	**-0.608**	-0.00205	0.0711	-0.345	-0.359	0.213	r
	0.00132*	0.99	0.754	0.105	0.0914	0.303	p*

* p<0.05 05 statistical significance level for Spearman correlation test

Due to scarce literature reports, the presented study may emerge as a pioneer investigation in the area of the pain of endometriomas.

Conclusions

It seems safe to conclude that chemokines and leptin may play a significant role in the occurrence of pain complaints among women with endometrial cysts. Further research might result in implementation of new treatment methods for pain management, especially in terms of pharmacotherapy.

Oświadczenie autorów:

1. Karolina Chmaj-Wierzchowska – autor koncepcji i założeń pracy, przygotowanie manuskryptu i piśmiennictwa, analiza statystyczna wyników – autor zgłaszający i odpowiedzialny za manuskrypt.
2. Małgorzata Kampioni – zebranie materiału, ostateczna weryfikacja i akceptacja manuskryptu.
3. Maciej Wilczak – ostateczna weryfikacja i akceptacja manuskryptu.
4. Stefan Sajdak – ostateczna weryfikacja i akceptacja manuskryptu.
5. Tomasz Opala – ostateczna weryfikacja i akceptacja manuskryptu.

Źródło finansowania:

Część projektu finansowanego z grantu KBN nr N N404 195037.

Konflikt interesów:

Autorzy nie zgłaszają konfliktu interesów i nie otrzymali żadnego wynagrodzenia związanego z powstawaniem pracy.

References

1. Alborzi S, Momtahan M, Parsanezhad ME, [et al.]. A prospective, randomized study comparing laparoscopic ovarian cystectomy versus fenestration and coagulation in patients with endometriomas. *Fertil Steril.* 2004, 82, 1633-1637.
2. Kotarski J, Polak G. Etiopatogeneza endometriozy. W: Ginekologia. Red. Słomko Z. Warszawa: *PZWL*. 2008, 303-308.
3. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis. *Fertil Steril.* 2008, 90 (Suppl 3), 60-69.
4. Lizuka M, Igarashi M, Abe Y, [et al.]. Chemical assay of iron in ovarian cysts: a new diagnostic method to evaluate endometriotic cysts. *Gynecol Obstet Invest.* 1998, 46, 58-60.
5. Glück J, Rymarczyk B, Rogala B. Zwiększone stężenie chemokiny CCL3/MIP-1 alfa w ciężkiej astmie oskrzelowej. Prz Med. *Uniw Resz Inst Leków.* 2011, 3, 287–290.
6. Gołąb J, Jakóbisiak M, Zagożdżon R, Obłąkowski P. Cytokiny. W: Immunologia. Red. Gołąb J, Jakóbisiak M, Lasek W. Warszawa: *Wydawnictwo Naukowe PWN.* 2006, 198-248.
7. Gmyrek GB, Sozanski R, Jerzak M, [et al.]. Evaluation of monocyte chemotactic protein-1 levels in peripheral blood of infertile women with endometriosis. *Eur J Obstet Gynecol Reprod Biol.* 2005, 122 (2),199-205.
8. Drosdzol-Cop A, Skrzypulec-Plinta V. Selected cytokines and glycodelin A levels in serum and peritoneal fluid in girls with endometriosis. *J Obstet Gynaecol Res.* 2012, 38 (10), 1245-1253.
9. Łuczak-Wawrzyniak J, Szczepańska M, Skrzypczak J. Ocena jakości życia kobiet z rozpoznaną endometriozą oraz sposobów radzenia sobie z negatywnymi skutkami choroby. *Prz Menopauzalny.* 2007, 6, 329–335.
10. Bedaiwy MA, Falcone T, Goldberg JM, [et al.]. Peritoneal fluid leptin is associated with chronic pelvic pain but not infertility in endometriosis patients. *Hum Reprod.* 2006, 21 (3), 788–791.
11. Bourdel N, Alves J, Pickering G, [et al.]. Systematic review of endometriosis pain assessment: how to choose a scale? Hum Reprod Update. 2014 Sep 1. pii: dmu046. [Epub ahead of print].
12. Burney RO. Biomarker development in endometriosis. *Scand J Clin Lab Invest.* 2014, 244, 75-81. [discussion 80. doi: 10.3109/00365513.2014.936692].
13. Burney RO. The genetics and biochemistry of endometriosis. *Curr Opin Obstet Gynecol.* 2013 Aug,25(4),280-6. doi: 10.1097/GCO.0b013e3283630d56.
14. Chmaj-Wierzchowska K, Pięta B, Czerniak T, Opala T. Endometriosis in a post-laparoscopic scar - case report and literature review. *Ginekol Pol.* 2014, 85 (5), 386-389.
15. Chmaj-Wierzchowska K, Kampioni K, Wilczak M, Opala T. Do inflammatory factors play a significant role in etiopathogenesis of endometrial cysts? Part 1. *Ann Agric Environ Med.* 2013, 20 (4), 854-858.