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## PECULIARITIES OF CLINICAL AND PARACLINICAL INVESTIGATIONS OF WOMEN WITH OVARIAN ENDOMETRIOMAS IN COMBINATION WITH PELVIC INFLAMMATORY DISEASE

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Endometriomas occupy a significant part in the structure of genital endometriosis. A clinical and paraclinical study of 210 patients with endometriomas was conducted. 57 patients (27.1 %) had newly detected endometrial cysts  $\leq 4$  cm, 46 women (21.9 %) had cysts  $> 4$  cm. Recurrent endometriomas  $\leq 4$  cm were detected in 71 patients (33.8 %), while  $> 4$  cm were in 36 women (17.1 %). A higher age, severe pelvic pain, and severe manifestations of external genital endometriosis were found in patients with recurrent endometriomas compared to those with newly detected endometrial cysts. In young women, unilateral endometriomas up to 4 cm in size are more often combined with a mild form of genital endometriosis, whereas in older patients endometrioid ovarian cysts, regardless of size, recur more often, are combined with severe manifestations of genital endometriosis, and are accompanied by impaired reproductive function.

**Key words:** endometrioma, pelvic inflammatory disease, pelvic pain, tumor markers, infertility.

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## ОСОБЛИВОСТІ КЛІНІКО-ПАРАКЛІНІЧНОГО ОБСТЕЖЕННЯ ЖІНОК З ЕНДОМЕТРІОМАМИ ЯЄЧНИКІВ ПРИ ПОЄДНАННІ ІЗ ЗАПАЛЬНИМИ ЗАХВОРЮВАННЯМИ ОРГАНІВ МАЛОГО ТАЗУ

Ендометріоми займають значну частку у структурі генітального ендометріозу. Проведено клініко-параклінічне обстеження 210 пацієнток з ендометріомами. У 57 пацієнток (27,1 %) вперше виявили кісти розміром  $\leq 4$  см, у 46 (21,9 %) – вперше виявлено кісти  $> 4$  см. Рецидивуючі ендометріоми  $\leq 4$  см діагностували у 71 (33,8 %), а розміром  $> 4$  см – у 36 жінок (17,1 %). Виявлено старший вік, виражений тазовий біль та важкі прояви зовнішнього генітального ендометріозу у пацієнток з рецидивуючими ендометріоїдними кістами яєчників порівняно з групами, де ендометріоми були виявлені вперше. У жінок молодого віку ендометріоми розміром до 4 см частіше поєднуються із легкою формою генітального ендометріозу, тоді як у пацієнток старшої вікової категорії ендометріоїдні кісти яєчників, незалежно від розміру, частіше рецидивують, поєднуються з тяжкими проявами генітального ендометріозу і супроводжуються порушенням репродуктивної функції.

**Ключові слова:** ендометріома, запальні захворювання органів малого тазу, тазовий біль, онкомаркери, безпліддя.

*The study is a fragment of the research project “Creation of diagnostic tactics and pathogenetic justification of effective methods of preservation and restoration of reproductive potential and improvement of parameters of quality of life of the woman with obstetric and gynecological pathology”, state registration No. 0121U109269.*

Genital endometriosis (GE) today remains one of the most common disease in women of reproductive age. The introduction of endoscopic diagnostic and treatment technologies has led to an increase in its share in the structure of gynecological problems from 5–10 % to 20–55 %. Among patients

of reproductive clinics, GE occurs in more than 30 %, while in case of chronic pelvic pain and infertility – up to 30–50 %, respectively [2, 8, 14].

The importance of one of the types of GE – ovarian endometrial cyst (OEC) – is difficult to overestimate, as existing surgical approaches do not eliminate the problem, do not profile recurrence, and reduce ovarian reserve, leading to ovarian dysfunction and infertility [3, 4, 8]. According to various authors, the proportion of ovarian endometriosis among operated women is up to 32 %; in every fourth case, the diagnosis of ovarian endometriosis was not verified before the surgery [4]. Ovarian endometrial cysts may be accompanied by serious reproductive dysfunction, and severe pain syndrome and are characterized by a significant recurrence rate [9].

The multifactorial nature of etiopathogenesis of chronic pelvic pain syndrome, resistance to therapy in patients with genital ovarian endometriosis in combination with pelvic inflammatory diseases (PID), and comorbid extragenital conditions are the actual interdisciplinary problems [9]. Chronic pelvic pain, oncophobia, as well as infertility, expand the indications for surgery, which also reduces the ovarian reserve, thereby contributing to reproductive aging and accelerating menopause [4].

Despite a large number of scientific publications devoted to the problems of endometriomas and pelvic inflammatory diseases, practically there is no research devoted to the study of the relationship between these two pathologies, and available publications are fragmentary [4]. Solving these problems is a real challenge for modern medicine, so it requires an in-depth study of the existing research materials and the development of possible promising issues for discussion with their subsequent solution.

**The purpose** of the study was to evaluate the clinical and paraclinical features of women of reproductive age with endometriomas combined with pelvic inflammatory disease, taking into account the size and recurrence of cysts.

**Material and methods.** A total of 210 women, aged 18–40 years with OEC, were studied and divided into the following groups. Group 1 included 57 patients (27.1 %) with newly detected OEC, size ≤ 4 cm; group 2 consisted of 46 women (21.9 %) with newly detected OEC, size > 4 cm; group 3 – 71 patients (33.8 %) with recurrent endometriomas, size ≤ 4 cm, group 4 consisted of 36 women (17.1 %) with recurrent OEC, size > 4 cm (fig. 1).

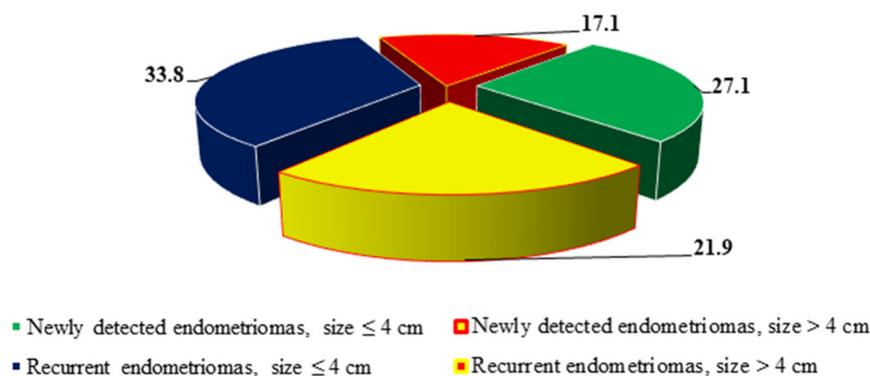


Fig. 1. Distribution of patients due to the size and nature of the ovarian endometriomas, n=210, %.

The control group included 20 relatively healthy women who applied to the clinic for surgical sterilization. It should be noted that all study groups also included a category of patients whose OEC was combined with pelvic inflammatory disease (PID), (50 people) (23.8 %). Chronic salpingoophoritis (58.0 %), chronic endometritis (24.0 %), and tuboovarian tumors (18.0 %) were dominant among the clinical types of PID.

The study was approved by the local Ethical Committee of the Ivano-Frankivsk National Medical University (approval ID 123/21 from 21.09.2021). The research was conducted following the principles of bioethics set out in the WMA Declaration of Helsinki – “Ethical principles for medical research involving human subjects” and “Universal Declaration on Bioethics and Human Rights” (UNESCO). All patients signed a voluntary consent to the proposed study. The following methods were used: analysis of general and gynecological history, gynecological examination, assessment of pain according to the visual analog scale (VAS), assessment of tumor markers CA-125 and 19-9, ultrasound, diagnostic hysteroscopy (if necessary), medical laparoscopy and morphological examination.

Statistical analysis of the obtained categorical data was performed using MS Excel (License № 100320004D878C8A) by calculating the frequency of signs and symptoms per 100 subjects, while the statistical significance in observation groups and null-hypothesis testing was performed by calculating Pearson's chi-squared test ( $\chi^2$ ). The parameters are presented as mean arithmetic value and mean standard deviation ( $\bar{x} \pm SD$ ). The differences between the selections were considered statistically reliable at  $p < 0.05$  (Tukey's test) [6].

**Results of the study and their discussion.** The mean age was  $34.5 \pm 2.6$  years. It should be noted that the part of older age category patients (36–40 years) in the group with recurrent OEC was significantly higher in comparison to the group where OEC was detected for the first time ( $p < 0.05$ ) (Tab. 1).

Table 1

**Distribution of patients by age and pain severity degree according to the VAS, (Abs. n. (%)), n=210**

Parameters	Newly detected OEC $\leq 4$ cm, n=57	Newly detected OEC $> 4$ cm, n=46	Recurrent OEC $\leq 4$ cm, n=71	Recurrent OEC $> 4$ cm, n=36
Age				
18–25 y.o.	11 (19.3)	10 (21.7)	7 (9.9)	1 (2.8)*
26–35 y.o.	24 (42.1)	16 (34.8)	23 (32.4)	10 (27.8)
36–40 y.o.	22 (38.6)	20 (43.5)	41 (57.7)*	25 (69.4)*
Pain severity degree				
Mild	16 (28.1)	8 (17.4)	6 (8.5)	9 (25.0)
Moderate	22 (38.6)	12 (26.1)	11 (15.5)	6 (16.7)
Severe	14 (24.6)	24 (52.2)	51 (71.8) <sup>o</sup>	20 (55.6)
Absence of pain	5 (8.8)	2 (4.3)	3 (4.2)	1 (2.8)

Note: \* – a significant difference compared to the data where OEC were detected newly (1<sup>st</sup> and 2<sup>nd</sup> groups) ( $p < 0.05$ ); <sup>o</sup> – a significant difference compared to the mild pain severity degree ( $p < 0.05$ ).

Among patients with a combination of OEC and PID, the age category of 36–40 years takes 64.0 % (32 people), which is significantly greater compared to the group with newly detected OEC ( $p < 0.05$ ).

Characterizing the leading symptoms, it is necessary to indicate that the pain syndrome had varying severity according to the VAS: mild pain was noted by 39 people (18.6 %); 51 women (24.3 %) indicated moderate pain, and, in more than half of the cases (109 patients – 51.9 %) severe pain, 11 (5.2 %) patients, mostly with small in size cysts, did not complain at all. Moderate pelvic pain was observed in almost equal proportions in patients with large cysts and small recurrent ovarian cysts; severe pelvic pain was significantly more common in patients with large recurrent endometriomas and in combination with PID.

Infertility complaints were noted in 142 patients (67.6 %). Statistically significant differences were established regarding the percentage of infertility in patients with primary OEC (51 – 43.5 %) against the data in the group with recurrent endometriomas (91 – 85.0 %) ( $p < 0.05$ ). In 57 cases (27.1 %) dyspareunia was observed without statistically significant differences in groups ( $p > 0.05$ ); the data on the frequency of dyshesia were also comparable (46 – 21.9 %).

It should be noted that in the group with OEC  $\leq 4$  cm, the part of patients with OEC in combination with PID take almost a third of the cases (16 – 28.1 %), while in the group with OEC  $> 4$  cm, the combination of those pathologies was not observed. In the groups with recurrent OEC, a combination of OEC and PID was also observed in almost a third of cases (34 – 31.8 %) ( $p < 0.05$ ).

Surgical treatment was performed in 153 patients (72.9 %) by laparoscopic access; 57 women (27.1 %) were monitored while in 29 cases (13.8 %) cyst puncture and sclerotherapy were used according to current guidelines [9]. There are indications for repeated surgery in every second case (107 cases – 50.9 %).

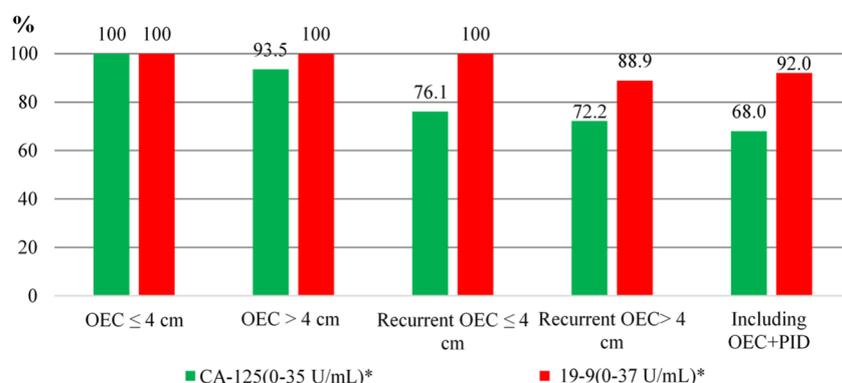


Fig. 2. The percentage of a woman with tumor marker level within reference value in all study groups, n=210. \* – normal (reference) value.

An increase of CA-125 beyond the reference values was noted in the case of recurrent OEC  $\leq 4$  cm and recurrent OEC  $> 4$  cm (23.9 % and 27.8 % retrospectively), as well as in the case of primary noted OEC  $> 4$  cm (6.5 %), while in women with primary OEC  $\leq 4$  cm, CA-125 marker values were within the reference (fig. 2).

Also, an increase in the level of CA-125 and 19-9 beyond the reference values was found in the combination of OEC with PID (32.0 % and 8.0 % retrospectively).

During the surgical treatment, in 153 patients a combination of OEC with objective signs of external genital endometriosis was confirmed: isolated cyst was observed quite rarely (in 14 cases – 9.2 %); severe manifestation of external genital endometriosis was diagnosed in 39 patients (25.5 %), as well as in case of recurrent OEC > 4 cm (19 – 12.4 %). In other cases, 1<sup>st</sup> and 2<sup>nd</sup> degrees of severity dominated (83 – 54.2 %) (tab. 2).

Table 2

**Distribution of external genital endometriosis manifestations, considering the characteristics and size of the endometrioma, n=153**

Study groups	Isolated ovarian endometrioma, (n=14)		Combination with external genital endometriosis of 1 <sup>st</sup> and 2 <sup>nd</sup> degree, (n=83)		Combination with external genital endometriosis of 3 <sup>rd</sup> and 4 <sup>th</sup> degree, (n=56)	
	Abs.n.	%	Abs.n.	%	Abs.n.	%
Primary OEC ≤ 4 cm	5	35.7	10	12.0	7	12.5
Primary OEC > 4 cm	3	21.4	17	20.5	13	23.2
Recurrent endometrioma ≤ 4 cm	4	28.6	24	28.9	17	30.4
Recurrent endometrioma > 4 cm	2	14.3	32	38.6*	19	33.9
Including a combination of OEC and PID	-	-	Including 11 – 13.3*		Including 39 – 69.6*	

Note: \* – the difference was statistically significant against the data of the group with isolated ovarian endometriosis (p<0.05).

It should be noted that all 50 patients with OEC in combination with PID were operated on. During the surgical treatment, severe (3<sup>rd</sup> and 4<sup>th</sup> degree) external genital endometriosis was detected in 78.0 % of cases, while mild and moderate (1<sup>st</sup> and 2<sup>nd</sup> degree) external genital endometriosis was detected in 12.0 % of cases (p<0,05). Severe manifestations of external genital endometriosis were also founded in half of the cases (52.7 %) in a group with recurrent OEC>4 cm in size.

At the same time, patients with cysts ≤ 4 cm, as well as young women, had manifestations of external genital endometriosis of 1<sup>st</sup> and 2<sup>nd</sup> degrees of severity. Isolated endometriomas without combination with other types of external genital endometriosis were diagnosed without statistical differences in groups, although their share was significant in the case of primary OEC, size ≤ 4 cm (35.7 %).

According to population studies conducted by the World Endometriosis Research Foundation (WERF), more than 176 million women of different ages suffer from endometriosis and the number is constantly growing, which classified this disease as a modern epidemic [14]. The authors agree that endometriosis is “getting younger” [11]. If two decades ago it was the problem mainly of women over 35 years old. Today the proportion of patients up to 35 years has increased. In addition, the proportion of recurrences is high: in surgically recovered patients 25–30 years old women – up to 43.3 %, 30–39 years old women – up to 22.5 % [13]. In our study, a statistically significantly older age (36–40 years) of patients with recurrent endometrioid cysts of the ovaries and in a combination of OEC with PID was established. According to Shemelko TL, Pedachenko NYu, a high proportion of combined gynecological diseases is verified in women with a history of endometriosis, in particular, cervical pathology – 26.9 %, uterine fibroids – 21.8 %, as well as chronic inflammatory diseases of the pelvic organs – 68.9 %, of which 53.9 % noted the ineffectiveness of anti-inflammatory treatment or its short-term effect [3]. Scientific data published by Orlova YuA, Martynenko VB, became another statement of the role of inflammation in the etiology of endometriosis in the presence of inflammatory diseases of the pelvic organs in the anamnesis. The authors confirmed in their work the hypothesis that endometriosis is a disease with an inflammatory etiology, which provokes the formation of adhesions even without a history of PID and surgeries [2]. According to the results of our study, severe manifestations of external genital endometriosis were found more often in the group with recurrent OEC > 4 cm in size.

At the present stage of scientific research, much attention is paid to immunological disorders in the occurrence, development, and recurrence of endometrioid cysts of the ovaries including the processes of immune inflammation and pathological neoangiogenesis at the systemic and local levels [15]. A well-known scientific fact is the presence of an increased concentration of proinflammatory mediators and cytokines in the peritoneal fluid, and the intrafollicular proinflammatory microenvironment in patients with endometriosis negatively affects the quality of oocytes and embryos [7, 12]. There is a perception that large endometrioid cysts of the ovaries develop in association with functional luteal and follicular cysts [10]. The frequency of chronic pelvic pain while having endometriosis is from 26 % to 80 %. Furthermore, according to Lytvynenko et al., non-specific pain syndrome is one of the main indications for surgical treatment of female reproductive system benign tumors [1]. It should be noted that these symptoms are not

specific and occur by inflammatory, tumor diseases of the uterus and appendages, which preserves the difficulty of diagnosis and the high frequency of untreated forms and “therapeutic disorders” in correctional programs [10]. Thus, the literature indicates the obscurity, controversy, and lack of coverage of many issues related to early clinical diagnosis of endometrioid cysts of the ovaries and causes of recurrence, and the need for further research is appropriate from the standpoint of the development of rational therapeutic tactics and prevention.

### Conclusions

1. The results obtained in this study showed a statistically significantly higher age in patients with recurrent endometrioid ovarian cysts, compared with the group where unilateral small cysts were first detected.

2. Another finding was that moderate and severe pain syndrome is more common in older patient groups, in women with recurrent large endometriomas, and in combination with pelvic inflammatory diseases.

3. In young women, unilateral endometriomas up to 4 cm in size are more often combined with a mild form of genital endometriosis, whereas in older patients endometrioid ovarian cysts, regardless of size, recur more often, are combined with severe manifestations of genital endometriosis, and are accompanied by impaired reproductive function.

4. The obtained results demonstrate the expediency of optimizing the diagnostic algorithm and reproductive tactics, considering such criteria as age, association with gynecological diseases, history of surgery, the severity of pain syndrome, cyst size, and characteristics of tumor marker.

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