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**POSTOPERATIVE SCAR ENDOMETROSIS: OPTIMIZATION  
OF DIAGNOSIS AND TREATMENT**

**321.13 – surgery**

**Summary of Ph.D. Thesis in Medical Sciences**

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This present Ph.D. thesis was elaborated at the Department of Surgery no. 1 "Nicolae Anestiadi" and the Laboratory of Hepato-Pancreato-Biliary Surgery of "Nicolae Testemitanu" State University of Medicine and Pharmacy PI, based on two clinics: Mother and Child Institute IMPH and Emergency Medicine Institute IMPH of the founding Consortium of the Doctoral School in Medical Sciences.

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## LIST OF ABBREVIATIONS

|         |   |
|---------|---|
| ARME    | - abdominal rectus muscle endometriosis   |
| C       | - Cytoplasm                               |
| CM      | - cellular membrane                       |
| CT      | - computed tomography                     |
| EHP – 5 | - Endometriosis Health Profile - 5        |
| EMI     | - Emergency Medicine Institute            |
| ER      | - estrogen receptors                      |
| IMC     | - Institute of Mother and Child           |
| IMPH    | - Institute of Medicine and Public Health |
| IS      | - Intensity Score                         |
| MPV     | - mean platelet volume                    |
| MRI     | - magnetic resonance imaging              |
| N       | - nucleus                                 |
| PR      | - progesterone receptors                  |
| PS      | - Proportion Score                        |
| PSE     | - postoperative scar endometriosis        |
| PVSE    | - perineal and vaginal scar endometriosis |
| QL      | - Quality of Life                         |
| TS      | - Total Score                             |
| USG     | - ultrasound imaging                      |

## THE RESEARCH CONCEPTUAL FRAMEWORK

**Actuality of the research topic:** Endometriosis was defined as a nosological entity, characterized by the presence of ectopic endometrial tissue outside the uterus [1]. Postoperative scar endometriosis (PSE) is an orphan disease (ORPHA:137820), which has been scarcely reported in specialized literature as through unique or limited clinical cases, being related to a number of current diagnostic and treatment challenges [2]. The etiology and pathogenesis of PSE represents controversial issues among researchers, thus leading to non-standardized treatment approaches [3]. However, the accuracy of clinical diagnosis, imaging methods and histopathological investigations might directly affect the incidence of PSE.

Till now, the incidence of PSE patients with obstetric and gynecological surgery history makes up 0.03-1.08% of cases [4]. PSE is more commonly conditioned by cesarean section (CS) [5]. However, the risk of developing PSE regarding the emergency or scheduled CS cases has not been studied yet.

The perineal and vaginal scar endometriosis (PVSE) is an extremely rare endometrial ectopia localized and determined in most cases of episiotomy [6]. Thus, it should be mentioned that no sufficient studies on the development of PSE, due to surgical interventions, have been performed so far. Considering that few research attempts have been carried out to highlight the risk factors responsible for developing PSE, a detailed study might contribute to prevention of this disease. The clinical features of PSE range from common symptoms, such as catamenial pain associated with an increased volume of the postoperative scar region, to absence of clinical signs that might be challenging for specialists to establish a preoperative diagnosis [7]. The non-specific clinical picture leads to diagnostic errors, whereas the diagnosis might be established only at the histological examination later on [8].

The preoperative diagnosis of PSE is a difficult issue, due to its resemblance to a wide range of benign or malignant tumors [9]. Therefore, the diagnosis of PSE needs to be considered, while differentiating abdominal wall tumors in women who have undergone a cesarean section. Currently, despite the wide range of diagnostic and treatment methods, there are no defined criteria for the diagnosis and treatment of PSE, thus stressing the importance of clinical suspicion in assessing an optimal treatment approach [10]. At present, a strong interest is shown to studying of the tumor marker CA-125, the preoperative mean platelet volume (MPV) indices and study of the peripheral systemic inflammatory response of the neutrophil/lymphocyte index in the diagnosis of peritoneal endometriosis. Additionally, no specialized literature data have been found on the importance of the serological markers in the diagnosis of PSE, thus justifying the actuality of the present study [11].

Considering the difficulty of diagnosing PSE, the current specialized literature has suggested using ultrasound imaging (USG), Doppler ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) for preoperative diagnosis of anterior abdominal wall endometriosis [12]. Unless specific imaging criteria and anatomical features of the PSE are available, the establishment of these criteria will contribute to the preoperative diagnosing of PSE, as well as to assessing the rational volume of the resected area.

Currently, surgery is considered the method of choice in the treatment and prevention of PSE recurrence and malignancy, which includes two stages: resection (via *en block* removal) and reconstruction (abdominal wall plasty) [13]. It has been established that R0 resection is the basic first-stage, which prevents disease recurrence. Current researches have revealed that further monitoring of patients with PSE allows determining the progression of the recurrent cases. [14].

However, there are a limited number of studies regarding the differentiated approach of the reconstructive stage, thus justifying the purpose of this present research paper.

The morphological assessment of the removed samples is extremely important for establishing the diagnosis of extragenital endometriosis [15]. According to recent studies on the immunohistochemistry methods used for diagnosing extrapelvic endometriosis, it is worth assessing the monoclonal antibodies (CD10, ER- $\alpha$ , PR, CK7, vimentin) in order to diagnose PSE [16]. Moreover, considering the present researches on assessment of the quality of life (QL) in patients with peritoneal endometriosis [17] and lack of specialized literature data on determining this index in PSE patients, further targeting studies are needed.

**The purpose of the research:** Optimizing the diagnosis and treatment management of patients with postoperative scar endometriosis by assessing a variety of clinical, imaging and morphological criteria, as well as the surgical treatment outcomes.

**The study objectives:**

1. To study the clinical manifestations of PSE and the characteristics of its localization.
2. To determine the types of previous surgeries and define the risk factors responsible for the development of postoperative scar endometriosis.
3. To establish the imaging method criteria (ultrasound, Doppler, computed tomography, and magnetic resonance scanning), as well as the anatomical and topographical features of postoperative scar endometriosis.
4. To assess the optimum surgical volume to solve postoperative scar endometriosis based on early and further outcomes.
5. To evaluate the morphological features and the immunohistochemistry profile of surgical scar endometriosis.

**Scientific research methodology:** The research paper is a prospective and retrospective study analysis of the diagnostic procedures and treatment results, assessed in 34 patients with PSE over a period of 26 years. A detailed information was obtained according to the approved questionnaire. The following methods were used within the present research: (1) clinical investigation and examination; (2) laboratory (blood biochemistry and tumor markers); (3) imaging (ultrasound + Doppler imaging, computed tomography, magnetic resonance scanning); (4) histopathology (light microscopy, immunohistochemistry profile). The following methods were used for statistical processing: Kolmogorov-Smirnov test, Student criterion, U criterion - Mann - Whitney test, Fisher's exact test, ANOVA test. Statistical data processing was carried out via GraphPad Prism 5.0 software (GraphPad Software, Inc.). The statistical data were rendered by graphical presentation.

**The scientific novelty and originality:** The primary risk factors of PSE occurrence were identified, based on clinical data assessment, viz: (1) cesarean section cases (89.3%,  $p < 0.0001$ ); (2) primiparous cases (80%,  $p < 0.0001$ ); (3) scheduled operations (76%,  $p = 0.0005$ ); (4) intact amniotic membrane (88%,  $p < 0.0001$ ).

There were found non-specific clinical signs, as well as constant pain, which was reported in 38.2% of cases ( $p > 0.05$ ) and inactive growth volume depending on the menstrual cycle in 29.4% cases, showing a statistically significant difference ( $p = 0.0014$ ), which requires a thorough differentiated diagnosis.

The study also highlighted the following PSE specific features: prevailing anterior abdominal wall cases (82.4%,  $p < 0.0001$ ), single endometriomas occurrence compared to multiple ones (91.2% vs. 8.8%,  $p < 0.0001$ ), Pfannenstiel incision vs. median laparotomy (92.3%

vs. 7.7%,  $p < 0.0001$ ), left-angle endometrioma incidence of Pfannenstiel laparotomy (75%) vs. right angle (16.6%) vs. bilateral (4.2%) vs. central (4.2%), showing a statistically significant difference ( $p = 0.0012$ ).

USG and Doppler have a major role in the diagnosis of PSE, as well as the following imaging criteria: round/oval – shaped growth masses, hypoechoic with hyperechoic contour and presence of vascularization (91.7%), showing a statistically significant difference ( $p = 0.0001$ ). The average diameter of the PSE was established according to the degree of vascularization, thus confirming that larger endometriomas are accompanied by a gradually increasing vascularization degree.

The MRI results in the diagnosis of PSE were analyzed by revealing the micro-hemorrhages occurring within both the growth mass and in marked perifocal inflammation, depending on the menstrual cycle, thus MRI scan procedure should be carried out before or immediately after the menstrual period.

The basic principles of surgical treatment were structured in order to prevent recurrent PSE cases, to maintain the integrity of the mass formation via *en bloc* surgical excision, exceeding 5–10 mm within healthy tissues. The criteria for reconstructing the abdominal wall, following an endometrioma excision were also developed.

For the first time, a number of particularities have been established, based on the PSE morphopathological assessment, which included (1) presence of active and inactive evolutionary forms; (2) presence of elastosis in the stroma and tissues; (3) unformed endometrial globoid cell mass located remotely from primary source; (4) the morphological aspects were similar to pseudoxanthoma, pseudomixoma or fibroelastoma. The PSE immunohistochemistry profile was characterized by positive expression in the endometrial glands (CK7, vimentin, PR, ER – $\alpha$ ) and in the cytogenic stroma (CD10, PR, ER – $\alpha$ ).

For the first time, the surgical intervention in patients with PSE has been successfully proven, by assessing the quality of life index, thus showing a significant further postoperative improvement of QL.

**The scientific issue solved within this thesis** is based on development and implementation of the diagnostic and treatment methodology of PSE, which will provide better treatment outcomes, prevent the disease relapse and improve the patient's quality of life.

**Theoretical significance of the study:** The detailed analysis enabled the reveal of potential risk factors responsible for PSE incidence. The research established the particular PSE-related imaging signs (USG, CT, MRI), and the degree of endometrioma vascularization. The serological assessment on CA-125 tumor marker values and the preoperative mean platelet volume and neutrophil/lymphocyte index proved that these index values are not characteristic for patients with PSE. There were identified the steps of the surgical treatment, R0 resection being considered the basic principle of the first stage, in order to prevent the disease recurrence. The reconstructive stage was performed depending on the size of the aponeurosis defect, thus in minor defects, synthetic sutures (tension free) were used for aponeurosis closure, whereas the major defects were reconstructed by applying a synthetic mesh. The morphological and immunohistochemical characteristics (CD10, PR, ER – $\alpha$ , vimentin, CK7, Ki67) of the PSE were also described. The monitoring was carried out by assessing the local status on the absence of relapse and postoperative hernia occurrence.

**The applicative value of the PhD thesis:** The specific and non-specific clinical features of PSE have been described within this present research. The study also conducted a careful

assessment of the clinical and imaging criteria that may help in differentiating diagnosis for tumors situated within postoperative scars. The PSE specific imaging signs (USG + Doppler, CT, MRI scanning) were revealed. The study described the surgical steps, applied for PSE treatment, as well as further surgical treatment outcomes, in terms of any potential recurrent cases, postoperative hernia incidence and its further impact on quality of life.

**Implementation of research findings:** This present study enabled the implementation of new methods of diagnosis and treatment of PSE-diseased patients, within the surgical departments, at the Emergency Medicine Institute, the Department of Surgical Gynecology, at the Institute of Mother and Child (IMC) (Chisinau, Republic of Moldova) and within the teaching process of the „Nicolae Anestiadi” Department of Surgery no.1, at „Nicolae Testemitanu” State University of Medicine and Pharmacy.

**Research findings approval:** The results of the study were reported and discussed at various national and international scientific events such as: the 33<sup>rd</sup> Balkan Medical Week (Bucharest, 2014); the 16<sup>th</sup> National Congress of Obstetrics and Gynecology (Cluj-Napoca, 2014); the 36<sup>th</sup> Annual Meeting of Surgeons from Moldova “Iacomi Răzeșu” and the 8<sup>th</sup> Surgery Conference with international participation (Piatra-Neamț, 2014); Annual Scientific Conference of IMPH Institute of Emergency Medicine on "*News and controversies in the management of medical and surgical emergencies*" (Chisinau, 2014); the 37<sup>th</sup> Meeting of Surgeons from Moldova (Piatra-Neamț, 2015); the Young Researchers Conference at the Institute of Emergency Medicine (Chisinau, 2015); the 12<sup>th</sup> Congress of the "Nicolae Anestiadi" Association of Surgeons from the Republic of Moldova, with international participation (Chisinau, 2015); La XX-ème Session des Journées Médicales Baalkaniques la deuxième séance scientifique commune avec L'Académie Nationale de Médecine de France (Paris, 2015); the 7<sup>th</sup> Congress of Surgeons from Russia on “Current Surgical Issues” (Rostov-on-Don, 2015); the 23<sup>th</sup> Congress of Surgeons from Ukraine (Kiev, 2015); the 4<sup>th</sup> Congress of the Romanian Society on Ultrasound in Obstetrics and Gynecology and the National conference on Medical Days, "Vasile Dobrovici" 13<sup>th</sup> edition (Iași, 2016); the 6<sup>th</sup> International Medical Congress for Students and Young Doctors MedEspera (Chisinau, 2016); the 5<sup>th</sup> National Congress of Surgery (Sinaia, 2016); the 29<sup>th</sup> International Congress in Endoscopy on "New technologies in the diagnosis and treatment of gynecological diseases" (Moscow, 2016); Young Researchers Conference at the Institute of Emergency Medicine (Chisinau, 2017); the International Scientific and Practical Conference on "Fundamental and applied research findings in the field of natural and technical sciences" (Belgorod, 2017); Young Researchers Conference at the Institute of Emergency Medicine (Chisinau, 2017); the Annual Scientific Conference of the IMPH Institute of Emergency Medicine on "News and controversies in the management of medical and surgical emergencies" (Chisinau, 2018); the 22<sup>th</sup> International Congress in Endoscopy on "New technologies in the diagnosis and treatment of gynecological diseases" (Moscow, 2019); the 13<sup>th</sup> Congress of „Nicolae Anestiadi" Association of Surgeons from the Republic of Moldova with international participation (Chisinau, 2019).

The PhD thesis results were discussed and approved at the meeting of „Nicolae Anestiadi” Department of Surgery no. 1, at „Nicolae Testemitanu” State University of Medicine and Pharmacy (protocol no. 4, dated on 22.11.2019), at the Scientific Seminar on Surgery (321.13), Pediatric Surgery (321.14), Urology and Andrology 321.22), and Transplantology (321.24) ” (protocol no. 10, dated on 10.06. 2020)

**Publications related to PhD thesis:** The obtained scientific results were published in 23 scientific articles, including one article in the International Journal indexing in the Web Science,

3 articles - in international journals, 5 articles - in National Register Journals, 11 materials / theses presented at international conferences abroad, 3 materials/theses - at international conferences (local). There are three no co-authorship publications, including three articles published within the journals.

**Summary of the thesis:** The thesis includes annotations in Romanian, Russian and English, a list of abbreviations, introduction, 4 chapters, synthesis of results, general conclusions, and practical recommendations. The bibliography included 274 sources, annexes, the declaration on author's responsibility, and the author's CV.

**Keywords:** postoperative scar endometriosis, abdominal rectus muscle endometriosis, catamenial pain, cesarean section, immunohistochemistry profile, perineal and vaginal scar endometriosis.

This present Ph.D. thesis received the positive opinion of the Research Ethics Committee within the „Nicolae Testemitanu" State University of Medicine and Pharmacy PI (protocol no. 57/40 dated on 13 February 2017).

### PhD THESIS CONTENT

**1. Modern aspects of the etiopathogenesis, diagnosis and treatment of postoperative scar endometriosis.** This chapter includes a detailed analysis and synthesis of current publications related to the topic of the thesis on the etiopathogenesis, diagnosis and treatment of PSE. Additionally, a detailed study of topic-related data was carried out, regarding the imaging methods for diagnosing PSE. The early and late PSE treatment outcomes were assessed, followed by a subsequent evaluation of postoperative patient quality of life.

**2. Research material and methods.** The research study was conducted within the Department of Surgery no. 1 „Nicolae Anestiadi" and Laboratory of Hepato-Pancreato-Biliary Surgery of „Nicolae Testemitanu" State University of Medicine and Pharmacy PI, based on two clinics: at the Department of Surgical Gynecology of Institute of Mother and Child (IMC) IMPH and at the Surgery Departments of Emergency Medicine Institute (EMI) IMPH, during a reference period of 1991-2017 years. This descriptive study is based on retrospective and prospective analysis of 34 cases with PSE, following different types of obstetric and gynecological surgeries.

The sample size calculation was based on data regarding PSE incidence, which accounted for 0.03–1.08% [4]. Since PSE rarely occurs, the required number of subjects enrolled within the study was estimated according to the following formula used for descriptive studies:

$n = P (1 - P) (Z\alpha/d)^2$ , whereas n - the representative sample size

P - the best studied estimating value

(1.08% - 0.0108)

Z $\alpha$  - table value equal to 1.96

d - distance or tolerance (0.05)

(1) Thus,  $n=0.0108 \times (1-0.0108) \times (1.96/0.05)^2=0.0108 \times 0.9892 \times 1536=16.41$  of patients, which revealed 10.0% non-responsive cases, whereas the representative sample size included 18 patients with PSE.

Prior to being included within the prospective study group, all patients agreed via an informed consent. Patients were selected based on the inclusion and exclusion criteria, that underwent clinical-anamnestic and paraclinical investigations based on the approved study



protocol. The study was authorized in accordance with ethical requirements, and received a favorable opinion of the Research Ethics Committee of „Nicolae Testemitanu" SUMPh, no. 57/40 dated on 13 February 2017.

The study inclusion criteria were as follows: (1) preoperative PSE diagnosis; (2) PSE diagnosis confirmed by imaging methods (USG + Doppler, CT, MRI scan); (3) morphological and immunohistochemical confirmation of PSE. Patients were aged between 22 – 44 years old, the average age being –  $30.1 \pm 0.9$  years (95% CI:28.23–32.06). The demographic structure is presented in figure 1.

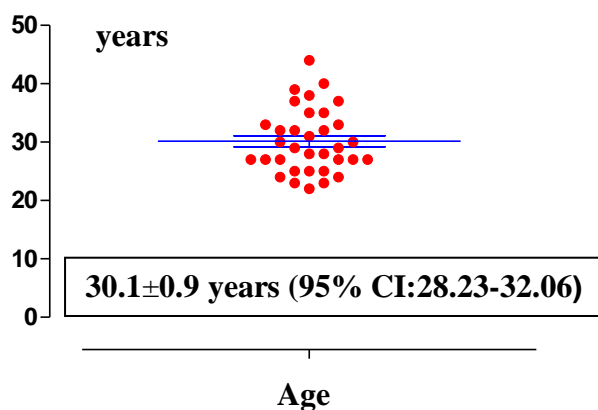


Figure 1. Demographic structure of PSE patients

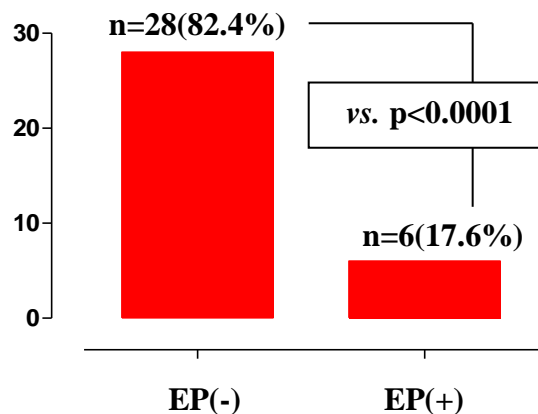


Figure 2. PSE associated with pelvic endometriosis

Depending on its localization, PSE was more commonly reported in the anterior abdominal wall (n=28) compared to the perineal region (n=6). According to PSE occurrence regarding surgical interventions on the abdominal wall, the following data were revealed: cesarean sections (n=25), myomectomies (n=1), laparoscopic interventions - laparoscopic ablation of the source of endometriosis by monopolar coagulation (n=1), diagnostic laparoscopy (n=1).

The average cesarean delivery term was estimated at  $37.7 \pm 0.4$  weeks (95% CI:36.85–38.59). Indications for emergency caesarean section (n=6) were as follows: severe preeclampsia (n=1), labor dystocia (n=1), acute fetal hypoxia (n=1), premature membrane rupture + pelvic presentation (n=2), placenta previa (n=1). Indications for scheduled caesarean sections (n=19) were as follows: pelvic presentation (n=7), duplex (n=2), transverse fetal lie (n=1), placenta previa (n=2), severe preeclampsia (n=3), uterine scarring (n=4).

Of the total number of patients with PSE (n=34) included in the study group, 6(17.6%) cases were associated with pelvic endometriosis, whereas 1 case exhibited stage I endometriosis, 3 cases – stage II endometriosis (n=3) and 2 patients – stage III endometriosis (n=2) (figure 2).

### Characteristics of laboratory and instrumental research methods

**Clinical methods.** The diagnosis of postoperative scar endometriosis was based on the past obstetrical gynecological surgery history, objective clinical examination (presence of tumor growth on the postoperative scar, the cyclical nature of pain, as well as on imaging and laboratory data.

**Laboratory methods.** All patients underwent the following laboratory investigations: ABO/Rh blood group assessment, Complete Blood Count + platelets, and neutrophil-to-lymphocyte ratio assessment (normal range –  $0.41 \pm 0.03$  CU).

**The tumor markers** were determined via the electrochemiluminescence immunoassay (ECLIA) by Siemens Immulite 2000 xp device (Germany), normal values being considered: CA – 125 (0–35 IU / L).

**Imaging methods. Ultrasound (USG) and Doppler scanning** were performed within the imaging units of IMPH IEM and IMPH IMC by Liliana Fuior-Bulhac, MD, PhD, by using Esaote MyLab 15, Sono Scape 8000 (China) and Toshiba Aplio 300 (Japan) devices and via 3-5 MHz transducer for transabdominal and 5-7.5 MHz - for transvaginal (rectal) examinations. The USG examination enabled to assess the three orthogonal diameters of each mass, to estimate the mean value, to determine the shape (oval/round), location (postoperative scar, adjacent region and perineum), depth (superficial/deep), to outline the characteristics (smooth/irregular). The echogenicity was compared with the normal adjacent subcutaneous tissue and surrounding tissue. The Doppler examination provided quantitative parameters of vascularization of the endometrioma according to two parameters: (1) the presence or absence of vascularization and its degree, (2) localization. The vascularization degree was assessed depending on the number of blood vessels feeding the tumor viz. no vessels (absent vascularization), 1-3 vessels (poor vascularization), 3-6 vessels (moderate vascularization), more than seven vessels (profuse vascularization) [18]. There were identified three types of vascularization, based on vessel distribution within the formation, such as: peripheral vascularization, occurring around the formation without any ramifications into the endometrioma; central vascularization occurring only inside; mixed - peripheral and central vessel distribution.

**Spiral computed tomography (CT)** was performed by SOMATOM Emotion Duo (Siemens, Germany), Siemens Somatom Sensation 64 CT Scanner (Siemens, Germany). CT assessed the following features: localization, depth, margin outlines, presence or absence of cysts within the mass, density (Hounsfield Unit - HU), associated scar tissue, multiplicity, and presence of coexisting intraperitoneal disease.

**Magnetic resonance imaging (MRI)** used Siemens MAGNETOM® Avanto 1.5T (Germany), Siemens MAGNETOM® Essenza 1.5T (Germany), Siemens MAGNETOM® Skyra 3T (Germany), AIRIS® Hitachi (Hitachi medical Systems America, Inc). The MRI examination assessed the size, location, its correlation with the adjacent tissues, the presence or absence of micro-hemorrhages inside the masses.

**The morphological methods.** The morphological assessment was performed by Vergil Petrovici, MD, Head of the Morphopathology Department, at IMPH IMC, and Ilie Țiple, MD, PhD, Head of the Department at IMPH IEM. Histological examination was performed using the scar-shaped tissue samples retrieved during surgery from patients with PSE in paraffin samples. Prior to that the material was fixed in 10% buffered neutral Formalin solution and subsequently 6 tissue samples were retrieved from each specimen, then processed according to the histological standards, by using the Diapath histoprocessor and Raffaello staining network (Italy). The histological tests (5-6 tests from each sample) were performed with a thickness of  $\approx 3.5\text{-}4\mu$  via SLEE MAINZ-CUT 6062 microtome (Germany). The staining procedure used the conventional hematoxylin and eosin (H&E), Van Gison (VG), and Masson trichrome (tcM) stains to estimate the connective tissue, as well as evaluation of elastic fibers pattern with orcein staining. Microscopic examination was performed via Axiolab microscope, Carl Zeiss (Germany) at magnification of  $\times 2.5$ ;  $\times 10$ ;  $\times 20$ ;  $\times 40$ .

**The immunohistochemical methods.** The immunohistochemical examination was studied and described by Inga Chemencedji, the head of the Morphopathology Department of IMPH

Institute of Oncology. The immunohistochemistry was performed on deparaffined 4  $\mu\text{m}$  thick sections. For unmasked reception, the bottles with sections in Tris buffered saline were heated in a water bath ( $t=97^\circ\text{C}$  for 40 min.). Endogenous peroxidase was blocked by incubating the sections in 3% hydrogen peroxide (for 15 min.). The immunohistochemical reactions were visualized by using EnVision FLEX Mini Kit, High pH (Dako®, Denmark). The sections were stained with hematoxylin. Positive control samples for each antibody were selected according to the manufacturer's specifications.

*Monoclonal antibody panel:*

- CD10 expression was assessed via monoclonal mouse antibodies (clones 56C6, DAKO®, Denmark);
- CK7 expression – via monoclonal mouse antibodies (1:50 dilution ratio, OV – TL 12/30 clones, DAKO®, Denmark);
- expression of progesterone receptors (PR) - monoclonal mouse antibodies (clones PgR636, DAKO®, Denmark);
- expression of  $\alpha$  estrogen receptors (ER- $\alpha$ ) - monoclonal mouse antibodies (clones 1D5, DAKO®, Denmark);
- Vimentin expression - monoclonal mouse antibodies (Clone V9, Dako®, Denmark);
- Ki-67 expression - monoclonal mouse antibodies (Clone MIB-1, Dako®, Denmark);

*Statistical processing* of quantitative values was performed by variational analysis model. The average value (M), the average error (m) and the confidence interval (95% CI) were calculated. The Kolmogorov – Smirnov test was used to determine the normal range of data distribution. In normal sampling distribution, the difference of mean samples-sizes was assessed via Student's t-test criterion. The Mann-Whitney U test was used in a statistically significant difference from normal distribution. The ANOVA test was used to compare the indices from the three groups. The Fisher's exact test was applied to compare the relative values. The results were considered statistically significant unless  $p < 0.05$ . Statistical data processing was performed with GraphPad Prism 5.0 software (GraphPad Software, Inc.).

### **3. CLINICAL AND IMAGING characteristics OF POSTOPERATIVE SCAR ENDOMETRIOSIS**

#### **3.1. Clinical signs of postoperative scar endometriosis**

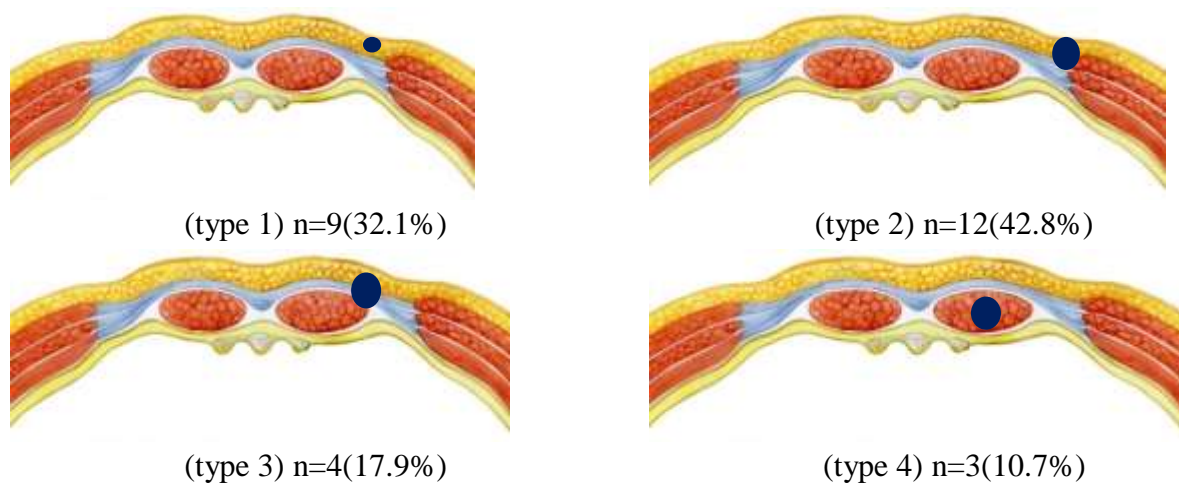
The average time of PSE onset in this present study, following a surgery, was  $44.1 \pm 2.6$  months (95% CI:38.72–49.46). Following a cesarean section –  $44.6 \pm 2.9$  months (95% CI:38.55–50.65), for gynecological surgeries -  $55.1 \pm 14.4$  months, for external genital surgeries -  $36.5 \pm 4.8$  months (95% CI:24.12–48.88), however their difference showed no statistically significant values ( $p=0.4502$ , ANOVA test). The time of pain onset occurring at the site of tumor formation was  $7.1 \pm 0.4$  months (95% CI:6.139–8.096) in the study group. This present study registered catamenial pain in 21(61.8%) patients and permanent pain in 13(38.2%), showing no statistically significant difference ( $p > 0.05$ ). Despite that catamenial pain is considered a pathognomonic sign for PSE, only a third of cases, included within the study, reported permanent pain that is not typical for this pathology, thus being difficult to diagnose. The increase in tumor volume, depending on the menstrual cycle, was observed in 24(70.6%) cases, whereas in 10(29.4%) cases it was absent.

According to PSE localization, there were determined the characteristic features for endometrial ectopias, which mostly occurred on the anterior abdominal wall – in 28(82.4%)

cases compared to the perineal region – 6(17.6%) cases, the findings showing a statistically significant value ( $p<0.0001$ ). This present study reported a number of endometriomas ( $n=38$ ), the higher incidence being found in single ones ( $n=31$ , 91.2%) compared to multiple endometrial ectopias ( $n=3$ , 8.8%), which were detected only in two cases *vs.* one case in the abdominal wall region and one case in the vaginal region ( $p<0.0001$ ). In the group with multiple endometriomas, two endometrial ectopias ( $n=2$ ) and three endometrial ectopias ( $n=1$ ) were reported.

The study on endometrioma locations, which correlated with postoperative Pfannenstiel incision scar ( $n=24$ ) was carried out: left angle ( $n=18$ , 75%), right angle ( $n=4$ , 16.6%), bilateral (right+left) – 1(4.2%), and central location – 1(4.2%). The predominant occurrence of the endometriotic source in the left angle of the scarring confirmed the theory of mechanical implantation, which is likely to be caused due to the surgeon position (obstetrician-gynecologist), mostly on the patient's left side, the left angle being difficult to access and thus being more vulnerable to contamination.

The PSE location within the anatomical structures of the anterior abdominal wall varies, being detected both in the superficial layers (type 1-3) and in the deep ones (type 4). There were reported 25 (89.3%) cases of superficial endometriosis *vs.* 3(10.7%) cases with deep localization, showing a statistically significant difference ( $p<0.0001$ ). Depending on PSE location ( $n=28$ ) within the anatomical layers of the abdominal wall, the following results were found: (type 1) which were located within the subcutaneous tissue; (type 2) involving the sheath of rectus abdominis muscle; (type 3) involving the muscles of the anterior abdominal wall; and (type 4) which were located in the rectus abdominis muscle – EMRA (figure 3).



**Figure 3. The structure of PSE localization in the anterior abdominal wall**

This study confirmed the prevailing occurrence of endometrioma, depending on the cesarean section incision: Pfannenstiel incision – 24(92.3%) cases compared to 2(7.7%) patients who underwent median laparotomy, showing a statistically significant value ( $p<0.0001$ ). Anterior abdominal wall scar endometriomas had a higher incidence in patients, who underwent a scheduled surgery – 19(76%) *vs.* emergency interventions 6(24%). Moreover, in cesarean section deliveries the amniotic membranes were found intact compared to low amniotic fluid cases – 22(88%) *vs.* 3(12%), ( $p<0.0001$ ). The anamnestic data analysis of patients with PSE revealed a higher incidence in primiparous patients - 20(80%) compared to multiparous patients - 5(20%), ( $p<0.0001$ ).

### 3.2. Ultrasound and Doppler imaging patterns of postoperative scar endometriosis

The patients with PSE, included within this study, underwent an ultrasound examination, which revealed round / oval-shaped tumor formations, hyperechoic fibrosis of irregular shape, presence of non-homogeneous, heterogeneous and hyperechoic fibrotic changes located at tumor peripheral margins (figures 4).

The patients complained of pain syndrome of a varying intensity, caused by the compression of the formation in the abdominal wall when the USG transducer was applied. The tumor size, depth and its correlation with nearby tissues were detected in all cases. Therefore, the USG examination was performed in 18(52.9%) cases, and USG + Doppler imaging in 12(34%) patients.

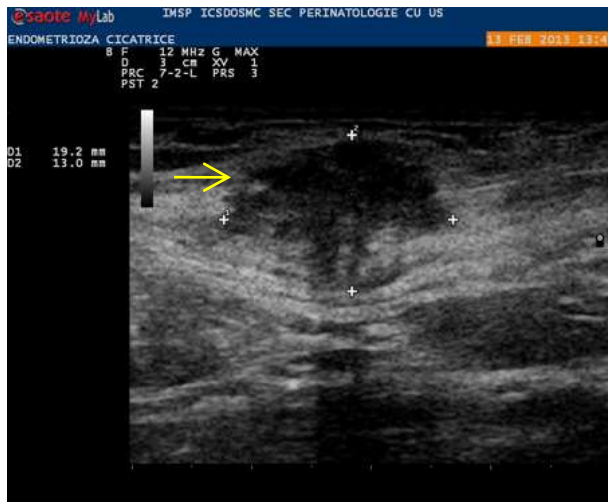


Figure 4. USG: hypoechoic nodule in the region of surgical scar (→)



Figure 5. Doppler ultrasound: mixed vascularization of the endometrioma

The USG examination revealed single endometrial nodules in 15(83.3%) cases vs. multiple nodules in 3(16.6%) cases. The largest endometrioma size was about  $23.9 \pm 2.7$  mm (95% CI:18.25–29.45), and the minimum size -  $15.9 \pm 2.1$  mm (95% CI:11.65–20.18). Vascularization of the formation was assessed by Doppler scan, which revealed vessels related to the cystic component. The Doppler examination enabled to determine vascularization in 11(91.7%) cases and lack of vascularization in 1(8.3%) case ( $p=0.0001$ ). These study findings allowed establishing the relevant prevalence of PSE with vascularization, compared to avascular endometriomas. The vessel diameter ranged between 1 - 2 mm, being on average -  $1.4 \pm 0.2$  mm. The degree of vascularization was determined in all case, according to the following scoring: 0 points (lack of vascularization) - 1(8.3%) case, 1 point (poor vascularization) - 7(63.6%) cases and 2 points (moderate and major vascularization) - 4(36.4%) cases. Thus, the PSE mean diameter with poor vascularization was  $20.6 \pm 3.3$  mm (95% CI:12.34–28.86), and the mean diameter in cases of PSE with medium and major vascularization was -  $40.1 \pm 2.9$  mm (95% CI:30.63–49.57), showing a statistically significant difference ( $p<0.05$ ) (figure 5).

### 3.3. The importance of computed tomography and magnetic resonance imaging in the diagnosis of postoperative scar endometriosis

CT and MRI were performed in 11(32.3%) patients enrolled within the study. CT examination determined isodense or hyperdense formations that ranged from the smallest-sized types, located within superficial layers, to endometriomas that were adjacent to the muscles and

showing a clear heterogeneous invasion (figure 6). The imaging examinations revealed solid irregular-shaped endometriomas located within postoperative lodge and extended to the adipose tissue, aponeurosis and rectal abdominal muscle. The size of the lesions located in the anterior abdominal wall ranged from 10 to 46 mm, whereas the mean native density was +44 U.H., post-contrast with moderate amplification up to +62 U.H. high sensitivity in detecting hemorrhagic sources on T1- weighted images were reported.



Figure 6. CT: abdominal wall endometrioma (→) Figure 7. MRI (T1): EMRA 28x23x21 mm (→)

The MRI Intravenous Contrast examination showed a reduced peripheral absorption in large formation. MRI is a more specific method than CT for diagnosing PSE due to the ability to better visualize the source with microhemorrhagic inclusions. The hyperintense sources on fat-suppressed T1-weighted images are due to mild hemorrhages. The presence of microhemorrhagic inclusions is a characteristic imaging sign for PSE (figure 7). The abdominal wall endometriosis is an isointense or high-intensity signal compared to the muscles presented on T2 and T1-weighted images. T1-weighted images with fat suppression are the most sensitive for detecting nodules smaller than 10 mm.

#### 4. SURGICAL TREATMENT OUTCOMES AND THE MORPHOPATHOLOGICAL FEATURES OF POSTOPERATIVE SCAR ENDOMETRIOSIS

##### 4.1 Features of surgical treatment and assessment of both postoperative remote outcomes and life quality in patients with postoperative scar endometriosis

The two stages of surgical treatment in PSE consist of resection and reconstruction. The average time of surgical treatment was about  $12.9 \pm 0.8$  days (95% CI:11.20–14.74) after the menstrual cycle. The surgical volume in most cases was determined preoperatively, based on the imaging results. The first stage was indicated in smaller formations, located in the superficial layers. The first stage technique is based on a full and complete excision of the endometrioma, thus preventing the disease recurrence.

The second stage consists of plastic reconstruction of the abdominal wall integrity for anterior abdominal wall aponeurosis, by using synthetic plastic material. Considering that the number of primiparous patients from the study group, aged -  $30.1 \pm 0.9$  years, was significantly higher (95% CI:28.23–32.06) absolute indications for applying a plastic mesh in order to minimize further risks were required only in cases of deep invasion into the muscular layers, followed by a large aponeurotic defect formation, which cannot be removed by tension-free

suturing. The following two options were suggested, depending on the size of the aponeurotic defect: synthetic suturing materials were used in minor aponeurotic defects (tension-free closure); reconstructive surgery was performed by using synthetic material in defects where this principle cannot be applied. *En block* excision was carried out by exceeding 5-10 mm within healthy tissue, while maintaining the formation intact, by removing the subcutaneous tissue. Depending on the endometrioma depth, excision was performed in 7(25%) cases, located subcutaneously, whereas 16(59%) cases required excision of the aponeurotic segment with tension-free sutures, using separate polypropylene threads. Anterior abdominal wall reconstruction by using a synthetic mesh was an absolute indication performed in 3(12%) cases, due to invasion into the peritoneal surface, thus causing a large aponeurotic defect, which couldn't be closed by tension-free sutures. Three cases of PSE (3/28 - 10.7%), associated with pelvic endometriosis (adenomyosis and endometriosis of the pelvic peritoneum) required simultaneous surgeries, such as: hysterectomy with PSE excision, resection of retrocervical endometriosis and laparoscopic excision of endometriotic source by monopolar coagulation. The average length of hospital stay was  $5.3 \pm 0.5$  days (95% CI:4.206–6.382), with no early postoperative complications. The average postoperative follow-up period of patients with PSE was  $28.7 \pm 1.8$  months (95% CI:24.95–32.40). Further patient surveillance lasted from 6 to 49 months and no recurrent PSE cases were reported. The local examination of the postoperative scars did not reveal the presence of hernias. The Endometriosis Health Profile - 5 (EHP-5) questionnaire was used to assess quality of life. According to the data presented in figure 8, the current study found a significant improvement in the quality of life of patients with PSE. The overall condition of patients showed an improvement in quality of life scores with a significant decrease in the mean scores from  $13.7 \pm 0.6$  (95% CI:12.37–15.11) to  $2.4 \pm 0.7$  (95% CI:1.205–3.742) postoperatively, which proved the benefits of surgical interventions.

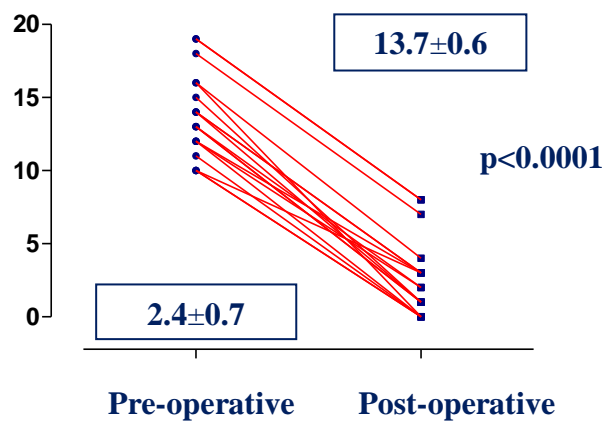


Figure 8. **Quality of life assessment**

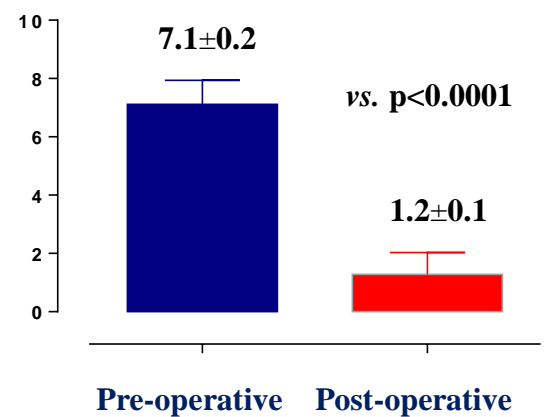


Figure 9. **Pre- and postoperative pain intensity**

In order to quantify pain intensity that directly affects the patient quality of life, the Wong-Baker faces pain-rating scale was used, whereas the preoperative mean score was  $7.1 \pm 0.2$ , and postoperative score -  $1.2 \pm 0.1$ , showing a statistically significant difference ( $p < 0.0001$ ) (figure 9).

#### 4.2. Morphological characteristics of postoperative scar endometriosis

The macro-microscopic study of colonized endometriotic scar tissue showed that, besides being typically characterized as ectopic endometriosis with cyclic morphological and functional features, it might change into a benign pseudonodular tumor with commonly progressive patterns due to invasion and reproduction aspects, causing the growth of the primary endometriotic

lesions. These changes characterize ectopic endometriosis and endometriotic tissues colonized as tumors, so called *abenign ectopic scar endometrioma*. The morphopathology used the term *benign ectopic endometrioma* within this study, characterized by the presence of typical endometrial-like tissue (gland with inactive epithelium, circumscribed by an insignificant cuff of endometriotic stromal vascular network) and transformations of the glandular, glandular-stromal and / or mixed structure through the cystic glandular component (figure 10).

Two evolutionary forms have been identified, depending on the morphological and morphopathological changes, the inactive and active forms. The inactive form is characterized by poorly outlined stromal cells, inactive glandular epithelium, poor vascularization and absence or presence of cyclic reactive capacities. The active form is featured by proliferative or polypoid patterns, presence of nuclear dysplasia without atypia, vascularized stroma and cyclic morphological and functional reactive capacities, suggesting a risk of developing a malignant tumor.

The present study also detected another phenomenon of aggressive endometrioma activity manifested by the presence of loop-like, non-formed endometriotic globoid formations located remotely from the primary source and endometriotic or stromal-glandular stromata, resembling endometriotic satellites, sited even in normally structural tissues. (figure 11).

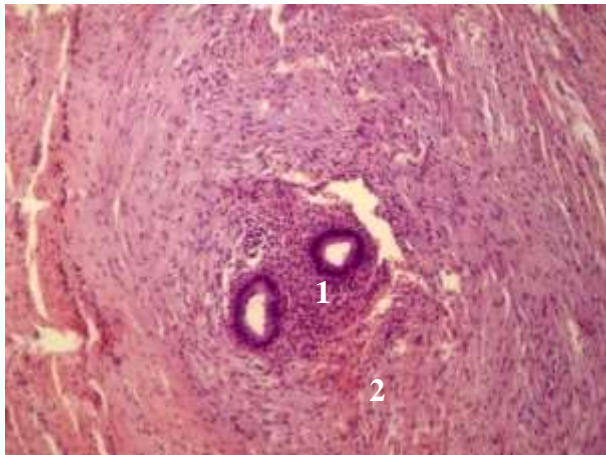


Figure 10. **Tubular glandular complex: (1) the epithelium reveals features of the early proliferative stage, (2) erythrocytosis in the stromal area (H&E × 75 staining)**

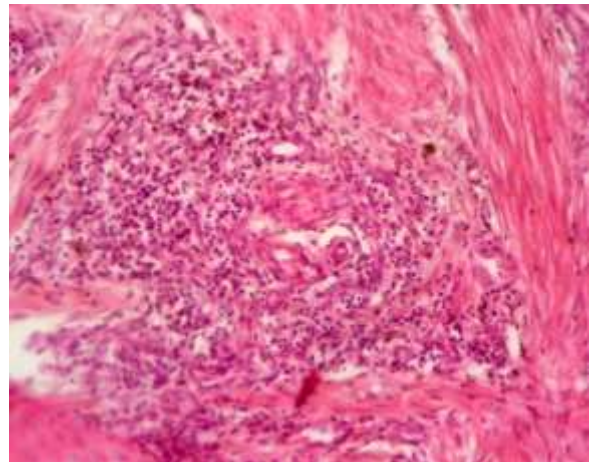


Figure 11. **Stromal-vascular loops with hemosiderosis and hemosiderophages, focal elastosis and lymphocytic infiltration (H&E staining × 150)**

This diagnosed phenomenon, in our opinion, represents the progressive activity of the endometrioma and requires special attention for the postoperative approach. Depending on the cyclic reactive capacities, the storage processes, inducing histiocytes, macrophage, pigmented histiocytes and hemosiderophages eactions, as well as on the intensity of the lymphocyte and polymorphonuclear inflammatory process, the benign endometrioma is characterized by presence of various glandular-stromal and colonized endometriotic pseudo or xanthomatous-like tissue and persistent inflammatory changes.

Another studied morphological feature was the presence of elastosis within the stroma and tissues that actually cannot be determined in a healthy endometrium. The elastosis can partially or completely replace the endometriotic source by involving the colonized tissues and their elasto-fibrosis changes, thus defining another morphological type such as fibroelastoma.



The histological diagnosis of ectopic endometriosis, particularly in scar endometriosis, is quite challenging, however its morphopathological features are highly important to consider, since it refers to a benign ectopic endometrioma, characterized by both inactive and active evolutionary features. The latter might be both progressive and invasive, resulting in endometriotic reminiscences after the removal of the primary focus. Another essential feature is that PSE can resemble to pseudoxanthoma, pseudomixoma, or fibroelastoma, which can be considered as evolutionary forms of postoperative scar endometriosis. Any presence or suspicion regarding the development of proliferative dysplastic processes might be predictive and suggestive of a malignant process.

#### 4.3. The immunohistochemistry profile of surgical scar endometriosis.

Due to PSE morphological changes that are sometimes difficult to identify, the immunocytochemistry assay was carried out, in order to confirm the diagnosis and determine the expression of CD10, progesterone receptors (PR), estrogen receptors (ER- $\alpha$ ), vimentin, CK7, Ki67, CD10 immunohistochemical examination with monoclonal antibodies showed an intense diffuse staining of the cytogenic stromal membrane (CM +++ ) and absence of endometrial cell staining (figures 12). In PR monoclonal antibodies, an intense staining of the nuclei of the endometrial gland and the membrane of the cytogenic stroma (N +++/CM +++ ) was identified (figure 13).

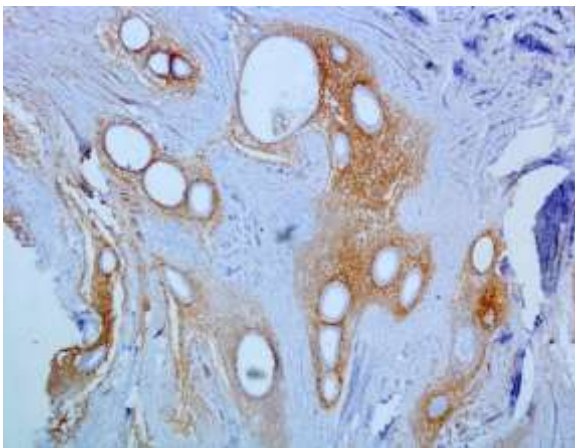


Figura 12. **Immunohistochemistry (CD10): diffuse expression of the cytogenic stromal membrane (DAB x 40)**

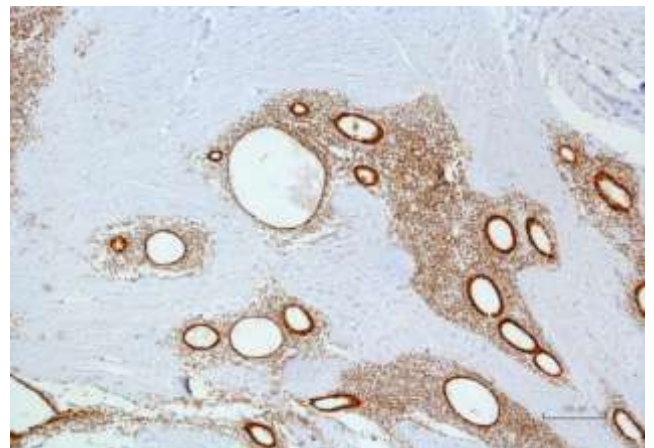


Figure 13. **Immunohistochemistry (PR): intense staining of nuclei within the endometrial glands and cytogenic stromal membrane (N +++ / CM +++ ) (DAB x40)**

The distribution of PR in PSE varied to  $95.4 \pm 0.9\%$  (95% CI:93.30–97.56). The assessment of ER- $\alpha$  expression showed staining of the epithelial gland cell nucleus (N ++ ) (figure 14). The mean Allred DC et.al. index (1998) was  $4.4 \pm 0.5$  (95% CI:3.240–5.530), the Proportion Score -  $3.1 \pm 0.4$  (95% CI:2.172–3.982), and the Intensity Score -  $1.3 \pm 0.1$  (95% CI:1.017–1.598). The immunocystochemical examination with CK7 revealed an intense, diffuse staining of the cytoplasm of the endometrial glands (C +++ ) in all cases, whereas no stromal staining was determined (figure 15).

In case the morphopathological assessment does not reveal complete data, the immunohistochemical examination by determining the expression of progesterone receptors

(PR), estrogen receptors (ER- $\alpha$ ), vimentin, CK7, Ki67 might help establish an accurate diagnosis as well as determine the appropriate resection amount of PSE.

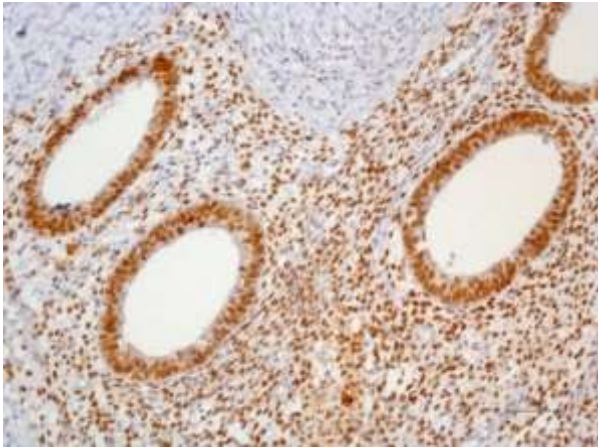


Figure 14. **Immunohistochemistry (ER- $\alpha$ ): nucleus staining of epithelial gland cells (N++) (DAB x200)**

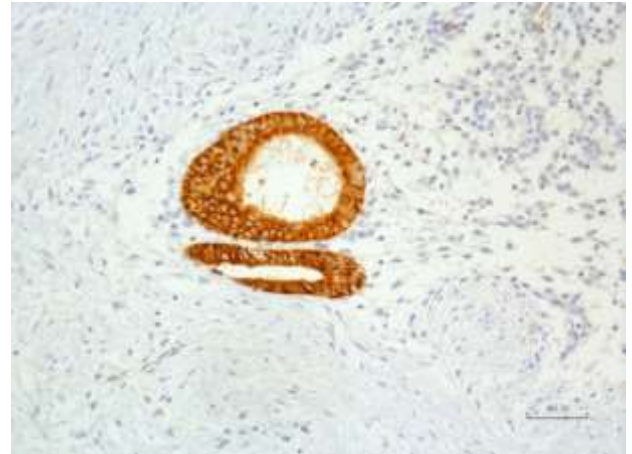


Figure 15. **Immunohistochemistry (CK7): diffuse staining of the cytoplasm of endometrial glands (C+++)(DAB x400)**

### GENERAL CONCLUSIONS

1. Clinical features were manifested by typical symptoms of catamenial pain in 61.8% of cases, and permanent pain in 38.2% of cases, that is not a pathognomonic sign for PSE ( $p>0.05$ ). An increase of the formation volume, depending on the menstrual cycle was reported in 70.6% of cases, compared to 29.4% of cases with no relevant signs, thus showing a statistically significant difference ( $p=0.0014$ ). The particular non-specific clinical signs require a very careful differential diagnosis of abdominal wall formations.
2. The obtained findings on the particularities of the PSE localization showed the following predominance: within the anterior abdominal wall *vs.* the perineal region (82.4% *vs.* 17.6%,  $p<0.0001$ ), Pfannenstiel incision *vs.* median laparotomy (92.3% *vs.* 7.7%,  $p<0.0001$ ), having a statistically significant difference. The Pfannenstiel's laparotomy revealed a prevailing occurrence in the left angle (75%) *vs.* right angle (16.6%) *vs.* bilateral (4.2%) *vs.* central (4.2%,  $p=0.0012$ ). According to endometrioma siting as related to the postoperative scar, the abdominal wall endometriomas were mostly found within the scar region (96.55%) compared to distant endometriomas (3.44%,  $p<0.0001$ ). Depending on the endometrioma localization within the abdominal wall layers, superficial siting was more commonly reported compared to deep localizations (89.3% *vs.* 10.7%,  $p<0.0001$ ).
3. As regarding the studies on the structure of surgical interventions contributing to development of PSE, the cesarean section surgeries were more commonly reported (89.3%) compared to traditional gynecological and laparoscopic interventions (10.7%,  $p<0.0001$ ). In PVSE cases, episiotomy was performed in 50% of cases *vs.* suturing postpartum ruptures - 33.3% *vs.* vaginal cyst removal - 16.6%. The following potential risk factors were found to be responsible for the development of PSE: cesarean section (89.3%,  $p<0.0001$ ), primiparous patients (80%,  $p<0.0001$ ), scheduled operations (76%,  $p=0.0005$ ), and intact amniotic membrane (88%,  $p<0.0001$ ).
4. The ultrasound and Doppler methods revealed the following PSE-related imaging criteria: round/oval-shaped volume mass, hypoechoic with hyperechoic contour, major endometrioma

size was on average  $23.9 \pm 2.7$  mm (95% CI:18.25–29.45); whereas the minor size –  $15.9 \pm 2.1$  mm (95% CI:11.65-20.18); presence of vascularization was found in 11 (91.7%) cases and 1(8.3%) case revealed no vascularization, thus showing a statistically significant difference ( $p=0.0001$ ). There were reported three types of PSE vascularization viz. peripheral, mixed, and central. CT study criteria characteristic for PSE were the homogeneous masses with presence of linear infiltration radiating peripherally to the neighboring subcutaneous tissue from the central node. MRI study criteria characteristic for PSE were the presence of micro-hemorrhagic inclusions.

5. The analysis of early and further surgical treatment outcomes revealed that the optimal surgical volume consists of the *en bloc* excision, exceeding 5-10 mm within the limits of healthy tissues, thus preserving the integrity of the mass. The superficially located endometrioma enables an extensive excision to be performed.
6. This present research determined the following morphological features: (1) presence of active and inactive evolutionary forms; (2) presence of elastosis within the stroma and tissues; (3) unformed endometriotic globoid formations located remotely from the primary source, resembling endometriotic or stromal-glandular stromal loops, defined as endometriotic satellites; (4) mimicry of the morphological features characteristic for pseudoxandoma, pseudomixoma or fibroelastoma. The immunohistochemical profile of PSE is characterized by positive expression in the endometrial glands (CK7, vimentin, PR, ER- $\alpha$ ) and in the cytogenic stroma (CD10, PR, ER- $\alpha$ ).

#### **Practical recommendations:**

1. The obstetric and gynecological surgeries, resulting in opening of the uterine cavity (cesarean section, myomectomy), require preventive measures for developing PSE, which should include: (1) externalizing the uterus from the abdominal cavity; (2) changing the meshes used to rehabilitate the uterine cavity; (3) using separate sutures when closing the uterus and the anterior abdominal wall layers; (4) using high-pressure irrigation for operative wound, while suturing the abdominal wall, particularly of the angles (in Pfannenstiel incision) by applying a considerable amount of saline solution.
2. Although PSE is a rare disease, it is worth being included in the differential diagnostic algorithm for major masses, located in the postoperative scar sites (infiltrated post-operative scar, ligature abscess, incisional hernia, granuloma, tumor processes) and in patients who have underwent obstetric and gynecological surgeries.
3. USG + Doppler ultrasound, CT and MRI scanning are recommended in patients that lack the classic symptoms of PSE, thus revealing the specific imaging signs for determining the degree of invaded adjacent tissues that might influence the assessment of the proper surgical volume.
4. The correlation between the MRI imaging characteristics for PSE, the micro-hemorrhages inside the nodules and a marked inflammation, depending on the periods of the menstrual cycle, might suggest the importance of MRI scanning before or immediately after menstrual cycle.
5. The surgical intervention based on the main concept of the resection stage, namely the *en bloc* excision, exceeding 5-10 mm within the limits of healthy tissues, while maintaining the integrity of the masses, might prevent the disease relapses. The reconstructive stage depends on the aponeurosis defect size by, applying the following options: polypropylene synthetic

sutures are used in minor defects, for tension-free closure of aponeurosis, whereas in large defects, the reconstruction is performed using synthetic materials due to impossibility to apply this method.

6. Morphopathological examination and immunohistochemical profile by determining the expression of progesterone receptors (PR), estrogen receptors (ER- $\alpha$ ), vimentin, CK7, Ki67 will allow establishing a final diagnosis and determining the appropriate degree of PSE resection.

*These practical recommendations are provided for specialists in the field of surgery, obstetrics and gynecology, imaging, morphopathology and immunohistochemistry, as well as for residents and senior students of State University of Medicine and Pharmacy.*

### SELECTIVE BIBLIOGRAPHY

1. Rindos NB, Mansuria S. Diagnosis and management of abdominal wall endometriosis: a systematic review and clinical recommendations. *Obstet Gynecol Surv.* 2017; 72(2):116-122.
2. Ozturk A, Kaya C, Bozkurtoglu H, Tan N, Yananli ZD, Ucmakli E. Scar endometrioma: an uncommon yet easily treated condition. *J Reprod Med.* 2016; 61(5-6):249-53.
3. Mistrangelo M, Gilbo N, Cassoni P, Micallef S, Faletti R, Miglietta C, Brustia R, Bonnet G, Gregori G, Morino M. Surgical scar endometriosis. *Surg Today.* 2014; 44(4):767-72.
4. Zhang P, Sun Y, Zhang C, Yang Y, Zhang L, Wang N, Xu H. Cesarean scar endometriosis: presentation of 198 cases and literature review. *BMC WomensHealth.* 2019;19(1):14.
5. Horton JD, Dezee KJ, Ahnfeldt EP, Wagner M. Abdominal wall endometriosis: a surgeon's perspective and review of 445 cases. *Am J Surg.* 2008;196(2):207-12
6. Aytac HO, Aytac PC, Parlakgumus HA. Scar endometriosis is a gynecological complication that general surgeons have to deal with. *Clin Exp Obstet Gynecol.* 2015;42(3):292-4.
7. Ecker AM, Donnellan NM, Shepherd JP, Lee TT. Abdominal wall endometriosis: 12 years of experience at a large academic institution. *Am J Obstet Gynecol.* 2014;211(4):363.e1-5.
8. Medeiros FC, Cavalcante DI, Medeiros MA, Eleutério J Jr. Fine-needle aspiration cytology of scar endometriosis: study of seven cases and literature review. *Diagn Cytopathol.* 2011;39(1):18-21
9. Erkan N, Hacıyanlı M, Sayhan H. Abdominal wall endometriomas. *Int J Gynaecol Obstet.* 2005;89(1):59-60.
10. Blanco RG, Parithivel VS, Shah AK, Gumbs MA, Schein M, Gerst PH. Abdominal wall endometriomas. *Am J Surg.* 2003;185(6):596-8.
11. Jegan A, Dimienescu O, Dull A. M. Noi markeri pentru diagnosticul non-invaziv în endometrioza. *Jurnal Medical Braşovean.* 2014;nr.2,p.39-41
12. Francica G. Reliable clinical and sonographic findings in the diagnosis of abdominal wall endometriosis near cesarean section scar. *World J Radiol.* 2012;4(4):135-40.
13. Zhang J, Liu X. Clinicopathological features of endometriosis in abdominal wall--clinical analysis of 151 cases. *Clin Exp Obstet Gynecol.* 2016;43(3):379-83.

14. Aubry G, Panel P, Thiollier G, Huchon C, Fauconnier A. Measuring health-related quality of life in women with endometriosis: comparing the clinimetric properties of the Endometriosis Health Profile-5 (EHP-5) and the EuroQol-5D (EQ-5D). *Hum Reprod.* 2017;1;32(6):1258-1269.
15. Zhu Z, Al-Beiti MA, Tang L, Liu X, Lu X. Clinical characteristic analysis of 32 patients with abdominal incision endometriosis. *J Obstet Gynaecol.* 2008;28(7):742-5.
16. Fukuda H, Hideki M. Cutaneous endometriosis in the umbilical region: the usefulness of CD10 in identifying the interstitium of ectopic endometriosis. *J Dermatol.* 2010;37(6):545-9.
17. Selcuk S, Sahin S, Demirci O, Aksoy B, Eroglu M, Ay P, Cam C. Translation and validation of the Endometriosis Health Profile (EHP-5) in patients with laparoscopically diagnosed endometriosis. *Eur J Obstet Gynecol Reprod Biol.* 2015;185:41-4.
18. Savelli L, Manuzzi L, Di Donato N, Salfi N, Trivella G, Ceccaroni M, Seracchioli R. Endometriosis of the abdominal wall: ultrasonographic and Doppler characteristics. *Ultrasound Obstet Gynecol.* 2012;39(3):336-40.

**• LIST OF THE AUTHOR'S PUBLICATIONS ON THE THESIS**

**• Articles published in international scientific journals:**

*✓ articles in Web of Science and SCOPUS international databases*

1. Mishin I., Mishina A., **Zaharia S.**, Zastavnitsky. G. Rectus Abdominis Endometrioma after Caesarean Section. *Case Rep Surg.* 2016:4312753.

*✓ articles published in recognized international scientific journals*

2. Ghidirim Gh., Mişin I., Mişina A., Rojnovceanu Gh., **Zaharia S.**, Chemencedji I. Endometrioza muşchilui rect abdominal. *Archives of the Balkan Medical Union.* 2015, vol.50, nr.2 (suppl. 1), pp.16-22. ISSN 0041-6940.
3. Mişina A., **Zaharia S.**, Mişin I., Petrovici V. Endometrioza cicatricială perineală și vaginală. *Archives of the Balkan Medical Union.* 2015, vol.50, nr.2 (suppl. 1), pp.70-75. ISSN 0041-6940.
4. **Zaharia S.** Endometrioza ombilicală. *Archives of the Balkan Medical Union.* 2016, vol.51, nr.1 (suppl. 1), pp.211-214. ISSN 0041-6940.

**• Articles published to accredited national scientific journals**

*✓ articles in B-category journals*

5. Mişina A., **Zaharia S.**, Mişin I., Fuior L., Petrovici V. Endometrioza cicatricei postoperatorii după operație cezariană. *Buletinul Academiei de Ştiințe a Moldovei Ştiințe Medicale.* 2014, nr. 3(44), pp. 122-126. ISSN 1857-0011.
6. **Zaharia S.** Transformarea malignă a endometriozei cicatricei postoperatorii. *Buletinul Academiei de Ştiințe a Moldovei Ştiințe Medicale.* 2015, nr. 4(49), pp. 73-77. ISSN 1857-0011.
7. Mişina A., **Zaharia S.**, Mişin I., Pochin A., Fuior-Bulhac L. Diagnostic preoperator al endometriomei cicatricei postoperatorii. *Buletinul Academiei de Ştiințe a Moldovei Ştiințe Medicale.* 2015, nr. 4(49), pp. 48-51. ISSN 1857-0011.

8. Mișina A., Mișin I., **Zaharia S.**, Chemencedji I. Endometrioza cicatriciei postoperatorii după miomectomie. *Buletin de Perinatologie*. 2016, nr.1(69), pp. 137-140. ISSN 1810-5289.
9. **Zaharia S.**, Mișina A., Mișin. I. Endometrioza cicatriciei postoperatorii complicată cu hemoragie externă: prezentare de caz. *Moldovan Journal of Health Sciences*. 2018, vol.15, nr.1, pp.93-101. ISSN: 23451-6705.

- **Abstracts/theses published within international scientific conferences**

10. **Zaharia S.**, Mishina A., Mishin I., Ghidirim Gh. Incisional endometrioma of the abdominal wall. *Archives of the Balkan Medical Union*.2014, vol.49, nr. (suppl. 1), p.A-130(P-105). ISSN 0041-6940.
11. Mișina A., **Zaharia S.**, Mișin I., Ghidirim Gh. Endometrioma cicatriciei postoperatorii cauzată de operația cezariană. *AlXVI-lea Congres Național al Societății de Obstetrică și Ginecologie din România*. Volum Rezumate. Cluj-Napoca, 2014, pp. 139-140. (P 15).
12. Ghidirim Gh., Mișin I., Mișina A., **Zaharia S.**, Gheorghită V. Endometrioma inciziei Pfannenstiel. *A XXXVI-a Reuniune a Chirurgilor din Moldova "Iacomi Răzeșu" și A VIII-a Conferință de Chirurgie cu participare internațională*. Volum Rezumate. Piatra-Neamț, România, 2014, pp.92-93.
13. Ghidirim Gh., Mișin I., Mișina A., **Zaharia S.**, Gheorghită V. Endometrioma cicatriciei postoperatorii a peretelui abdominal: douzeci și patru cazuri consecutive. *A XXXVII-a Reuniune a chirurgilor din Moldova "Iacomi – Razesu"*. Piatra-Neamț, 2015, Volum de Rezumate. pp.85-86. ISBN:978-606-13-2460-6.
14. Ciobanu Gh., Ghidirim Gh., Mishin I., Mishina A., **Zaharia S.** Les particularites dudiagnosticet du traitement chirurgicaldel'endometriose de la cicatricepostoperatoire.*La XX-ème Session des Journées Médicales Baalkaniques la deuxième séance scientifique commune avec L'Académie Nationale de Médecine de France*. Paris, 2015, Programme/Livre des Résumés. A63 (T5-05). ISSN 0041-6940.
15. Гидирим Г.П., Мишин И.В., Мишина А.Е., **Захария С.Л.** Эндометриоз послеоперационного рубца передней брюшной стенки. *XXIII з'їздї хїрургїв України. Збїник наукових робїт.«Клінічна хїрургїя»*. Київ, 2015, с.73. ISSN 0023-2130.
16. Гидирим Г.П., Мишин И.В., Мишина А.Е., **Захария С.Л.** Эндометриоз послеоперационного рубца. *Альманах Института хирургии имени А.В.Вишневского*. 2015, №2, с.371-372. ISSN 2075-6895.
17. Mișina A., **Zaharia S.**, Ghidirim Gh., Ghimpu V., Mișin I. Postoperative scar endometriosis: 31 consecutive cases. În: *Al 13-a Ediție a Conferinței Naționale Zilele Medicale "Vasile Dobrovici" și al 4-lea Congres al Societății Române de Ultrasonografie în Obstetrică și Ginecologie*. *Ginecologia.ro Journal*. 2016, nr.11 (suppl.1). p.83. ISSN 2344-2301.
18. Ghidirim Gh., Mișin I., Mișina A, **Zaharia S.**, Vasilev V. Endometrioza cicatriciei condiționată de operația cezariană. *Congresul Național de Chirurgie*. Sinaia, România, 2016, pp. 260-261.
19. Мишина А.Е., Гидирим Г.П., Мишин И.В., **Захария С.Л.**, Васильев В.Е. Эндометриоз передней брюшной стенки после кесарева сечения. В: *XXIX Международный Конгресс с курсом эндоскопии «Новые технологии в диагностике и лечении гинекологических заболеваний»*. Москва, 2016, с.154-155. ISBN:978-5-906484-18-5

20. **Захария С.Л.** Эндометриоз послеоперационного рубца. *Международной научно-практической конференции*. Белгород, 2017, с.91-94.

• **Abstracts/theses published within national scientific conferences**

21. Ghidirim Gh., Mișin I., Mișina A., **Zaharia S.** Particularități de diagnostic și tratament chirurgical al endometriozei cicatricei postoperatorii. *Arta Medica*. 2015. nr.3(56). pp.41-42. ISSN 1810-1852.

22. **Zaharia S.**, Mișin I., Mișina A., Fuior-Bulhac L., Cuțitari I., Crăciun V. Endometrioza cicatricei postoperatorii: caracteristici Doppler-ultrasonografice. *Al IV-lea Congres al Medicilor Imagistici din Moldova cu participarea internațională. The Moldovan Medical Journal. Special Edition*. 2018. pp.87-88. ISSN 2537-6373.

23. **Zaharia S.**, Mișin I., Mișina Ana, Petrovici V. Particularitățile morfologice caracteristice endometriozei cicatricei postoperatorii. *Al XIII-lea Congres al Asociației Chirurgilor "Nicolae Anestiadi" din Republica Moldova, cu participare internațională. Arta Medica*. 2019. nr. 3 (72). p. 178. ISSN 1810-1852.

## ADNOTARE

Zaharia Sergiu „**Endometrioza cicatricei postoperatorii: optimizarea diagnosticului și tratamentului**”. Teza de doctor în științe medicale, Chișinău, 2020. Teza este expusă pe 120 pagini, conține - introducere, 4 capitole, sinteza rezultatelor obținute, concluzii, recomandări practice, 5 tabele, 110 figuri, 274 surse bibliografice. La tema tezei au fost publicate 23 lucrări.

**Cuvinte-cheie:** endometrioza cicatricei postoperatorii (ECP), endometrioza mușchiului rect abdominal, endometrioza perineală, dureri catameniale, operație cezariană, profil imunohistochimic.

**Domeniu de studiu:** 321.13 – chirurgie

**Scopul lucrării:** Optimizarea managementului diagnostic-curativ al pacientelor cu endometrioza cicatricei postoperatorii prin analiza variată a criteriilor clinice, imagistice, morfologice și a rezultatelor tratamentului chirurgical.

**Obiectivele lucrării:** (1) studierea manifestărilor clinice și particularităților de localizare a ECP; (2) determinarea structurii intervențiilor precedente și definitivarea factorilor de risc cauzatori de dezvoltarea ECP; (3) stabilirea criteriilor imagistice (ultrasonografice (USG), dopplerografice (DG), tomografice (TC), imagistice prin rezonanță magnetică (IRM), și a particularităților anatomo-topografice ale endometriozei cicatricei postoperatorii; (4) determinarea volumului optimal al intervenției chirurgicale în endometrioza cicatricei postoperatorii bazate pe studierea rezultatelor precoce și la distanță; (5) determinarea particularităților morfologice și a profilului imunohistochimic ale endometriozei cicatricei postoperatorii.

**Noutatea și originalitatea cercetării:** În baza evaluării clinice au fost stabiliți factorii de risc principali de dezvoltare al ECP. Studiul prezent a demonstrat prezența semnelor clinice nespecifice. Au fost stabilite următoarele particularități caracteristice ECP: predominarea în regiunea peretelui abdominal anterior, dominarea endometriomelor unice, mai frecvent în incizia Pfannenstiel cu prevalența unghiului stâng a cicatricei postoperatorii. Au fost determinate criteriile imagistice de diagnostic (USG, DG, TC și IRM), cu aprecierea informativității înalte a acestor metode în diagnosticul ECP. Au fost dovedite principiile de bază a tratamentului chirurgical al ECP: păstrarea integrității formațiunii și excizia chirurgicală *en bloc* (R<sub>0</sub>). Elaborate criteriile aplicării metodei de reconstrucție a peretelui abdominal după excizia endometriomului. Studiate particularitățile morfologice și imunohistochimice (CD10, RE- $\alpha$ , RP, CK7, vimentin) al ECP. Evaluate rezultatele tratamentului chirurgical al ECP la distanță, și apreciate calitatea vieții a pacientelor cu ECP conform scorului EHP-5.

**Problema științifică** soluționată constă în elaborarea și implementarea metodologiei de diagnostic și tratament al ECP, care va contribui la ameliorarea rezultatelor, prevenirea recidivei, și îmbunătățirea calității vieții.

**Semnificația teoretică:** S-au stabilit factorii potențiali de risc ce favorizează apariția ECP. A fost justificată importanța metodelor imagistice în depistarea și stabilirea diagnosticului de ECP preoperator. Studiată informativitatea testelor serologice (markerului tumoral CA-125, valorilor preoperatorii a volumului mediu trombocitar, și indexul neutrofil/limfocitar) în diagnosticarea ECP. Specificate principiile de bază ale tratamentului chirurgical al ECP. Determinat rolul examenului morfologic și profilului imunohistochimic în stabilirea definitivă a diagnosticului de ECP.

**Valoarea aplicativă a lucrării:** Sunt argumentate și formulate principiile diagnosticului și a tratamentului chirurgical al ECP.

**Implementarea rezultatelor științifice:** În baza cercetării, au fost implementate noi metode de diagnostic și tratament a pacienților cu ECP în secțiile de chirurgie IMSP Institutul de Medicină Urgentă (Chișinău, Republica Moldova), în secția de ginecologie chirurgicală IMSP Institutul Mamei și Copilului (Chișinău, Republica Moldova) și în procesul didactic al catedrei de chirurgie nr. 1 „Nicolae Anestiadi” a Universității de Stat de Medicină și Farmacie „Nicolae Testemițanu”. Au fost obținute 5 acte de implementare în practică.



## РЕЗЮМЕ

Захария Сергей «**Эндометриоз послеоперационного рубца: оптимизация диагностики и лечения**». Диссертация на соискание ученой степени кандидата медицинских наук, Кишинев, 2020. Диссертация изложена на 120 страницах, состоит из введения, 4 глав, синтеза полученных результатов, выводов, практических рекомендаций, 5 таблиц, 110 рисунков. Библиография включает 274 источника. По теме диссертации опубликовано 23 печатных работ.

**Ключевые слова:** эндометриоз послеоперационного рубца (ЭПР), эндометриоз прямой мышцы живота, перинеальный эндометриоз, катамениальные боли, кесарево сечение, иммуногистохимический профиль.

**Область исследования:** 321.13 – хирургия

**Цель работы:** Оптимизация лечебно-диагностического менеджмента больных с ЭПР на основе многостороннего анализа клинических, радиологических, морфологических критериев и результатов хирургического лечения.

**Задачи исследования:** (1) изучить клинические манифестации и особенности локализации ЭПР; (2) определить структуры предшествующих операций и факторов риска, влияющих на развитие ЭПР; (3) установить радиологические признаки (на основании ультрасонографии (УСГ), доплерографии (ДГ), компьютерной томографии (КТ) и магнитно-резонансной томографии (МРТ) и анатомо-топографические характеристики ЭПР; (4) определить оптимальный объем хирургического вмешательства при ЭПР на основании изучения ближайших и отдаленных результатов; (5) изучить морфологические особенности и иммуногистохимический профиль ЭПР.

**Новизна и оригинальность исследований:** На основании оценки клинического материала установлены основные факторы риска ЭПР. Данное исследование продемонстрировало наличие неспецифических клинических симптомов при ЭПР. Были установлены характерные особенности ЭПР: преимущественная локализация в области передней брюшной стенки, преобладание единичных эндометриом, чаще при лапаротомии по Пфанненштилю и преимущественно локализуются в левом углу послеоперационного рубца. Установлены радиологические (УСГ, ДГ, КТ и МРТ) признаки ЭПР и определена высокая информативность методов при данной патологии. Определены основополагающие принципы хирургического лечения ЭПР: сохранение целостности эндометриомы и ее иссечение *en bloc* (R<sub>0</sub>). Разработаны критерии реконструкции передней брюшной стенки после иссечения эндометриомы. Изучены морфологические и иммуногистохимические (CD10, RE-α, RP, CK7, vimentin) характеристики ЭПР. Оценены отдаленные результаты и качество жизни (балльная система EHP-5) после хирургического лечения ЭПР.

**Решенная научная проблема** состоит в разработке и внедрении методологии диагностики и хирургического лечения ЭПР, что способствует улучшению результатов, профилактики рецидивов и улучшению качества жизни.

**Теоретическая значимость:** Установлены факторы риска развития ЭПР. Обоснована важность радиологических методов в визуализации и диагностике ЭПР. Изучена информативность серологических тестов (онкомаркера СА-125, среднего количества тромбоцитов и нейтрофильно-лимфоцитарного индекса) в диагностике ЭПР. Установлена роль морфологических и иммуногистохимических методов в окончательной диагностике ЭПР.

**Практическая значимость:** Аргументированы и сформулированы основные принципы диагностики и хирургического лечения ЭПР.

**Внедрение научных результатов:** На основании данного исследования внедрены новые методы диагностики и лечения пациенток с ЭПР в хирургических отделениях ПМСУ Института ургентной медицины (г. Кишинев, Республика Молдова) и в отделении оперативной гинекологии ПМСУ Института матери и ребенка (г. Кишинев, Республика Молдова), а также в педагогическом процессе кафедры хирургии №1 им. Н. Анестиади Университета медицины и фармации им. Н.Тестемицану. По результатам исследования получены 5 свидетельств по внедрению в медицинскую практику.

## ANNOTATION

Zaharia Sergiu, “**Postoperative scar endometriosis: optimization of diagnosis and treatment**” PhD Thesis, Chisinau, 2020. This research work comprises 120 pages, including introduction, 4 chapters, synthesis of the obtained results, conclusions, practical recommendations, 5 tables, 110 figures, and 274 bibliographic sources. The research findings were published with in 23 scientific works.

**Key-words:** postoperative scar endometriosis (PSE), endometriosis of rectus abdominis muscle, perineal endometriosis, catamenial pain, cesarean section, immunohistochemistry profile.

**Research domain:** 321.13 – surgery

**The purpose of the study:** To provide optimal diagnostic and treatment management of the patients with PSE by assessing a range of clinical, imaging and morphological criteria, as well as surgical treatment outcomes.

**The research objectives:** (1) To study the clinical manifestations and localization features of PSE; (2) to determine the past surgery structure and define the causative risk factors for PSE; (3) to establish the imaging criteria (ultrasound, Doppler, CT, MRI scan) and the anatomical and topographical features of postoperative scar endometriosis; (4) to determine the optimal surgical volume in PSE based on the study of early and long-term results; (5) to determine the morphological features and immunohistochemistry profile of PSE.

**Novelty and scientific originality:** The main risk factors for PSE development were identified based on the clinical assessment. The present study has demonstrated the presence of nonspecific clinical signs. The following features have been established: the predominance on the anterior abdominal wall region, dominance of single endometriomas, incision of Pfannenstiel, left angle of the Pfannenstiel laparotomy. The diagnostic criteria (ultrasound, Doppler, CT, MRI) were determined, which proved to be highly informative in the diagnosis of PSE. There have been proven the following basic principles of surgical treatment in PSE: preserving the integrity of the structure; en bloc surgical excision. There were developed the criteria for applying the method of reconstruction of the abdominal wall, following the endometrioma removal. The morphological features and the immunohistochemistry profile of the PSE were also studied. Both the long-term treatment outcomes and quality of life, based on EHP-5 score, were assessed within this research.

**The scientific issue to be solved** consists of development and implementation of the PSE diagnostic and treatment approach, which help improve patient outcomes, prevent relapses, and enhance quality of life.

**Theoretical significance:** This research paper identified the potential risk factors, leading to the onset of PSE. The importance of the imagistic methods for the preoperative diagnosis has also been justified. The serological tests (tumor marker CA-125, preoperative values of the mean platelet volume and neutrophil to lymphocyte ratio) proved to be highly informative in diagnosing PSE. The basic principles of the surgical treatment were specified. This research emphasizes the morphological features and immunohistochemistry profile for definite diagnosis of PSE.

**The applicative value of the research:** The research findings formulated and justified the principles of PSE diagnosis and surgical treatment.

**Implementation of scientific results:** The study results enabled implementation of the new methods of diagnosis and treatment of the PSE patients with in the surgical units, at Emergency Medicine Institute (Chisinau, Republic of Moldova), Department of Gynecology Surgery, Department of Research, at the Health Care Institute of Mother and Child (Chisinau, Republic of Moldova) and within the teaching process of „Nicolae Anestiadi” Department of Surgery No.1, at „Nicolae Testemitanu” State University of Medicine and Pharmacy. Five certificates have been obtained to be implemented into practice.