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DIAGNOSIS AND SURGICAL TREATMENT OF OVARIAN CYSTS AND TUMORS IN CHILDREN AND ADOLESCENTS

321.15 - OBSTETRICS AND GYNECOLOGY

Summary of Ph.D. Thesis in Medical Sciences

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The Ph.D. thesis was developed within the IMPH Mother and Child Institute (at Surgical Gynecology Department), members of the founding Consortium of the Doctoral School in Medical Sciences

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CONTENT

ABBREVIATIONS

ACS	abdominal compartment syndrome	**OL**	ovarian leiomyoma
AFP	α-fetoprotein	**MCT**	mature cystic teratoma
rAFS	revised American Fertility Society classification	**MRI**	magnetic resonance imaging
AT	adnexal torsion	**MRKH**	Mayer-Rokitansky-Kuster-Hauser syndrome
b-hCG	beta human chorionic gonadotropin	**MOT**	malignant ovarian tumors
BLOT	borderline ovarian tumor	**NLR**	neutrophil-lymphocyte ratio
BMI	Body Mass Index	**OC**	ovarian cyst
BOT	benign ovarian tumor	**OE**	ovarian endometriomas
CA 125	carcinoma antigen 125 or carbohydrate antigen 125	**OE(SOE)**	ovarectomy (salpingoovarectomy)
CA 19-9	carbohydrate antigen 19-9, cancer antigen 19-9	**OET**	ovarian epithelial tumors
CEA	carcinoembryonic antigen	**OMC**	ovarian mucinous cystadenoma
CIK	compositional index after King A.	**OMT**	ovarian mucinous tumors
CK-7	citokeratin 7	**OSS**	ovarian-sparing surgery
CK-20	citokeratin 20	**OT**	ovarian tumor
CT	computed tomography	**PLAP**	placental alkaline phosphatase
FIGO	The International Federation of Gynecology and Obstetrics	**POC**	paraovarian cyst
FOC	follicular ovarian cysts	**PpOC**	papillary ovarian cystadenoma
H.U.	Hounsfield units	**ROC**	receiver operating characteristic
IAHS	intra-abdominal hypertension syndrome	**SCA**	serous cystadenoma
I/R	ischemia / reperfusion	**SOT**	stromal ovarian tumors
Ki-67 (MIB-1)	proliferation index	**SSOC**	simple (serous) ovarian cyst
LAEC	laparoscopically -assisted extracorporeal cystectomy	**UMI**	ultrasonographic "morphological" index
LIC	laparoscopic intracorporeal cystectomy	**USG**	ultrasonography

CONCEPTUAL RESEARCH FRAMEWORK

Topic actuality

Recent studies show that ovarian cysts are a fairly common pathology in patients of different age groups. In children and adolescents, ovarian tumors are recorded in 2.6 cases per 100,000 [5]. In the vast majority of cases, ovarian tumors in children and adolescents are benign, the incidence rate of malignant neoplasms being about 10% [1, 22].

Description of the research situation and definition of research issues

Currently, imaging studies (ultrasound, CT, MRI) are considered the methods of choice in the diagnosis and assessment of ovarian cystic and tumor formations, as well as in the risk stratification strategy of malignant neoplasms [13]. One of the priority areas should be considered the researches on the development of unique radiological schemes for describing and stratifying the ovarian masses [14, 15], the information content of which in children decreases due to their age-related characteristics.

Assessment of the level of tumor markers (AFP, b-hCG, CA-125, CEA and CA19.9) in ovarian tumors among children is widely used to differentiate benign and malignant ovarian tumors. The acquired collective experience has confirmed the nonspecificity of the tumor marker values in the stratification of OT in children and adolescents, while their role remains quite controversial [22].

Adnexal torsion (AT) is considered among the most serious complications of ovarian cysts and tumors associated with the preservation of fertile function [3]. Currently, there are priority areas in the diagnosis of AT to be outlined, such as determining the clinical predictors of ATs [7], developing a scoring system [7, 16], assessing the specific ischemic and inflammatory serological markers for AT, as well as evaluating the role of the radiological methods (US imaging velocimetry Doppler, CT and MRI) in diagnosing AT [8]. In this regard, the prospects and actuality of the present research in the field of accuracy of various methods for the early diagnosis of AT are well defined.

The fundamental method of AT treatment involves the ovarian surgery (detorsion + cystectomy), regardless of the degree of ischemia [6, 10]. At the same time, there are ongoing studies related to the technical aspects of detorsion and the prevention of ischemia/reperfusion syndrome. Of particular interest are the unique publications concerning the structural and functional state of the ovaries after detorsion [11]. Despite the foregoing, the frequency of the unreasonable ovariectomies in torsion of the appendages accounts for 40%, according to the specialized literature [13].

Surgery is the treatment of choice for OT and symptomatic cystic masses refractory to hormone therapy in children. More and more experience are being gained in the application of laparoscopic technologies to this patient group [1, 2]. The main limitation in performing laparoscopic ovarian surgery in some cases is the large mass size, which significantly reduces the surgical space in the abdominal cavity. In this regard, alternative methods are being developed, like laparoscopically-assisted extracorporeal resections. However, only unique cases of using this method in children have been published in foreign literature so far [23].

Therefore, the diagnosis and surgical treatment of cystic and tumor formations in children and adolescents is an urgent issue of modern surgical gynecology. The scientific, practical and social significance of the present problem is determined by the development of a medical diagnostic complex aimed at increasing the number of organ-preserving surgeries and maintaining the fertile function.

The purpose of the study is to improve the surgical outcomes for ovarian cysts and tumors in children and adolescents based on the optimization of treatment and diagnostic strategies, as well on the assessment of early and remote treatment results.

Objectives of the research:

1. To study the particularities of clinical manifestations of ovarian cysts and tumor masses in children and adolescents.
2. To determine the imaging features of the ovarian cysts and tumor masses in pediatric patients.
3. To assess the information content of tumor markers in the diagnosis of ovarian tumors in children and adolescents.
4. To assess and improve the technical aspects of laparoscopic and classical organ-sparing operations for cystic and ovarian tumor masses in pediatric patients, as well as in uterine adnexal torsions.
5. To study the morphological structure and immunohistochemical profile of ovarian cystic and tumor masses in children and adolescents.

Research methodology. The paper is a descriptive study on the analysis of the diagnosis and surgical treatment of 267 pediatric patients (≤19 years old) with ovarian cysts (OC) and tumors (OT), who underwent surgeries within the Department of Surgical Gynecology of the Institute of Mother and Child (Chisinau, Republic of Moldova) from January 2000 to March 2019. The following research methods were used: (1) clinical research methods; (2) laboratory methods (blood biochemistry, determination of tumor markers); (3) imaging techniques (USG, CT, MRI); (4) endoscopic methods (laparoscopy); and (5) morphopathological methods (light microscopy, scanning electron microscopy, immunohistochemistry). The following methods were used for statistical processing: Kolmogorov-Smirnov test, Student's test, Mann-Whitney test, Fisher's exact test, ANOVA test, Kaplan – Meier prediction using the log-rank test (Mantel-Cox).

Novelty and scientific originality of the results obtained.

The comparison of the ultrasound parameters in ovarian mucinous cystadenoma (OMC) showed that, they exceed those of serous cystadenoma (SCA) both in terms of tumor size ($p=0.0862$) and tumor volume ($p<0.05$), as well as by the ultrasonic "morphological" index ($p<0.0001$).

It was found that, in the distribution of mature ovarian teratomas according to the classification of Jeoung HY, et.al. (2008), there were statistically significantly higher values ($p<0.0001$) recorded in classes B and C, compared with A and D. It has been shown that the liquid content of MCT increases the concentration of the CA19.9 tumor marker, which should be considered as the main increasing factor of this marker in blood during preoperative assessment.

It has been established that in adnexal torsions from both sides, medial torsion was statistically significantly more common ($p<0.0001$) than lateral torsion, the frequency being 31(86.1%) *vs.* 5(13.9%) cases. It has been proved that it is beneficial to carry out a dosed (staged) detorsion in AT, to level the I/R syndrome and to perform cyst-(tumor-)ectomies on the ovaries with maximum preservation of ovarian tissue in pediatric patients. The recovery time of the ovarian tissue color in AT depended on the degree of ischemia (II *vs.* III) and amounted to 24.2±1.8 min. (95% CI:19.97–28.53) compared to 32.8±0.8 min. (95% CI:30.83–34.73) ($p=0.0058$). The development and implementation of the detorsion technique in AT allowed a

statistically significant increase (p= 0.0054) in the number of ovary-preserving surgeries from 35.2% at the initial stage of the study to 84.2% at the final research stage.

It has been shown that primary mucinous ovarian tumors (OMT) , such as OMC, are characterized by the following features: (1) unilateral tumors; (2) macroscopically - multi-locular cystic masses; (3) size> 10 cm; 4) immunohistochemical profile – CK-7+ / CK-20- / CEA-; whereas the following signs are characteristic of secondary OMT: 1) bilateral tumors; (2) mostly solid in consistency; (3) size <7 cm; (4) immunohistochemical profile – CK-20+ / CEA+ / CK-7–. These forms of OT should be considered as metastatic tumors of low-grade appendiceal mucinous neoplasms and may potentially be associated with the development of abdominal pseudomyxomas.

Histopathological examination of MCT in children showed that mesodermal tissues were more commonly recorded than ectodermal and endodermal tissues, whereas the tissue derivatives, such as vascular (blood/lymphatic) and fibro-fatty ones were found in all cases of MCT.

On the basis of histopathological data, paraovarian cysts were characterized by (1) a predominance of 62.9% of mesothelial cysts lined with coelomic epithelium of peritoneal type; (2) a cyst of paramesonephric origin (Müllerian) was found in 29.6%; (3) in 1.9% of cases of mesonephric origin (Wolf); (4) 3.8% were characterized by the presence of dimorphic epithelium (mesothelial and Müllerian type); (5) a proliferative papillary cystadenoma was established in one case (1.9%) at the borderline of malignancy *(serous borderline).*

The scientific problem solved referred to the development of a methodology for rational approaches to the diagnosis, stratification and optimal surgical treatment of ovarian cysts and tumors in children and adolescents, aimed at enhancing the performance of ovarian operations and maintaining the reproductive function.

Based on immunohistochemical studies by using monoclonal antibodies CK-7 (clones OV-TL 12/30), CK-20 (clones Ks20.8) and CEA (clones II-7), the immunohistochemical profile of primary mucinous OT and secondary (low-grade appendiceal mucinous neoplasms) was defined. The histopathological structures of MCT tissues are described in detail according to the occurrence rate of the embryonic layer (ectodermal, mesodermal, endodermal) in children and adolescents. The composition of the elements of bone-dental structures from MCT is presented based on scanning electron microscopy (raster) with X-ray spectral microanalysis of a solid material performed via the X-ray dispersive spectroscopy. The case of ovarian dysgerminoma in Mayer-Rokitansky-Küster-Hauser syndrome (MRKH) is presented in detail. The case of proliferative papillary cystadenoma on the verge of malignancy (serous borderline type) is documented, which is the fourth case of this tumor in pediatric patients previously published in the literature.

Applicative value of the research: The clinical manifestations of ovarian cysts and tumors in children are thoroughly described. The imaging signs of different OC and OT groups in children and adolescents are carefully presented according to the USG, CT and MRI examination data. The use of CT and MRI in the algorithm of preoperative diagnostics is argued, which allows: (1) to sufficiently carefully stratify cystic and ovarian tumors in children by the mass size, radiological patterns and presence of a solid component (benign and malignant); (2) to determine the surgery method (laparotomy *vs.* laparoscopy); (3) to choose the surgical approach (Phannenstiel laparotomy *vs.* median laparotomy); (4) to plan the volume of surgery (cystectomy *vs.* ovariectomy).

The results of the use of tumor markers (AFP, CA–125, CEA and CA19.9) for ovarian cysts and tumors in children and adolescents have been thoroughly discussed, along with the percentage of their false-negative and false-positive results. The technical aspects of the ovary-preserving surgeries in case of OC and OT are also presented in detail. The technical aspects of surgical interventions for large ovarian masses in children, including those with AT, giant ovarian masses (> 15 cm), mucinous ovarian tumors, paraovarian and parasitic cysts, etc., have been highlighted. The study described in detail the surgery stages by using laparoscopic technologies, including the laparoscopically-assisted extracorporeal cyst-(tumor-)ectomies. The morphological structure of OC and OT in children and adolescents have been also thoroughly discussed. The present research described the surgical treatment outcomes of cystic and tumor masses in children.

Implementation of scientific results. Based on this study, new methods of treatment of pediatric patients with ovarian cysts and tumors were implemented at the Department of Surgical Gynecology, Department of Pediatric Gynecology, Department of Emergency Pediatric Surgery of IMSP Institute of Mother and Child (Chisinau, Moldova), as well as in the educational process within the Department of Obstetrics and Gynecology, Discipline of Obstetrics and Gynecology, Department of Pediatric Surgery, Orthopedics and Anesthesiology at "Nicolae Testemitanu" University of Medicine and Pharmacy.

The research approval. The main research principles were submitted and discussed at various national and international scientific forums: 33rd Balkan Medical Week (Bucharest, 2014); 16th National Congress of the Romanian Society of Obstetrics and Gynecology (Cluj-Napoca, 2014); Annual scientific conference at the IMPH Institute of Emergency Medicine "News and controversies in the management of medical and surgical emergencies" (Chisinau, 2017); The International All-Russian Surgical Forum (Moscow, 2018); 4th Congress of the Society for Endometriosis and Uterine Disease (SEUD) (Florence, 2018); 4th Congress of the Society for Ultrasound in Obstetrics and Gynecology (Bucharest, 2018); Annual Conference of Young Specialists of the Institute of Emergency Medical Care "Indicators and prospects of medical and surgical emergency care" (Chisinau, 2018); 4th Congress of Visual Physicians of Moldova with international participation (Chisinau, 2018); XXII International Congress with a course of endoscopy “New Technologies for Diagnosis and Treatment of Gynecologic Diseases” ; VI Congress of Obstetrics and Gynecology with International Participation (Chisinau, 2018); National Congress of the Romanian Society of Obstetrics and Gynecology (Iasi, 2018); Conferences of the Regional Institute of Oncology (Iasi, 2018); XIII International Congress on Reproductive Medicine (Moscow, 2019); VII Congress of the Society for Ultrasound in Obstetrics and Gynecology (Targu Mures, 2019); XXII Congress of the Society of Endoscopic Surgery of Russia (ROES named after Academician V.D. Fedorov) (Moscow, 2019); XXXII International Congress with the course of endoscopy "New Technologies for Diagnosis and Treatment of Gynecologic Diseases"; XIII Congress of the Association of Surgeons "Nicolae Anestiadi" of the Republic of Moldova with international participation (Chisinau, 2019); Annual scientific conference of the Institute of Mother and Child (Chisinau, 2019); 1st International Congress of Gynecological Oncology (Bucharest, 2020); Congress dedicated to the 75th anniversary from the foundation of the "Nicolae Testemitanu" SUMPh (Chisinau, 2020).

The research works were awarded the 1st-degree diplomas within the VI Congress of the Society of Ultrasound in Obstetrics and Gynecology (Bucharest, 2018) and the 1st International Congress of Gynecological Oncology (Bucharest, 2020).

The thesis results were discussed and approved at the joint meeting of the Department of Obstetrics and Gynecology along with the Scientific Laboratory of Perinatology of the Department of Surgery, Orthopedics and Pediatric Anesthesiology of Nicolae Testemitanu State University of Medicine and Pharmacy, Protocol no. 2 of September 8, 2021), Scientific Seminar in Obstetrics and Gynecology (321.15) (Protocol no. 4 of January 21, 2022).

Publications on thesis topic: 27 scientific papers were published on the thesis topic, of which 1 article – in journals abroad, 7 articles in national journals, 13 – materials/abstracts at international conferences (abroad), 7– materials/abstracts at international conferences in the republic.

Summary of the thesis compartments. The thesis includes a list of abbreviations, an introduction, 4 chapters, a summary of the results obtained, general conclusions, and practical recommendations. The bibliographic index comprises 295 sources, annexes, the statement of responsibility, the author's CV, 21 tables, and 133 figures.

Key words: children, adolescents, ovarian cysts, benign, malignant tumors, ovarian tumors, ovarian torsion, ischemia/reperfusion, tumor markers, ultrasound, dopplerography, computed tomography, magnetic resonance imaging, surgical treatment, laparoscopic ovarian cystectomy, surgery.

When developing the Ph.D. thesis, a positive conclusion was received from the Committee on Research Ethics at the PI Nicolae Testemitanu State University of Medicine and Pharmacy (Minutes no. 48/64 dated April 17, 2017).

CONTENT OF THE THESIS

1.Modern aspects of diagnosis and treatment of ovarian cysts and tumors in children and adolescents.

This compartment comprises the data of current publications on the thesis topic regarding the frequency, clinical manifestations and classification of cystic and tumor formations in children and adolescents. The research has highlighted the informativeness of the tumor markers in the diagnosis of cystic and tumor formations in children. There was performed a detailed analysis of similar studies on the information content of imaging methods in the diagnosis of ovarian cysts and tumors in pediatric patients. The present research also analyzed the literature data regarding the modern approaches to the surgical treatment of cystic and tumor formations in children and adolescents.

2. Research material and methods. The present research paper is a descriptive study on the diagnosis and surgical treatment of 267 children (≤19 years old) with ovarian cysts and tumors (OC and OT) who underwent surgery within the Department of Surgical Gynecology of the Institute of Mother and Child (Chisinau, Moldova) from January 2000 to March 2019.

According to the National Bureau of Statistics of Moldova, the female population rate aged 19 ranges from 362.036 (2019) to 593.622 (2000). According to the worldwide literature, the incidence rate of developing large ovarian tumors in children and adolescents is 2.6/100,000 [29]. The maximum possible size of the total cohort is 199 potential patients. Considering a 95% confidence interval (z-index = 1.96) and an error margin of 5%, the obtained sample size required (sample size) 131 observations to be included in the study.

The study framework involved the following concepts: "children’s age" (people under 18 years old) as defined by the United Nations Convention on the Rights of the Child, and "adolescence" (aged from 10 to 19 years old), as recommended by the United Nations Children's

Fund (UNICEF)/World Health Organization (WHO)/United Nations Population Fund (UNFPA), mean body mass index (BMI), Tanner puberty, menstrual status.

Criteria for inclusion in the study group: (1) patients aged ≤ 19 years; (2) functional ovarian cysts that do not disappear after conservative treatment (tending to increase, higher intensity in symptoms, like pain and compression); (3) benign and malignant ovarian tumors in patients of this age group; (4) availability of informed consent signed by the subject and a third party. Exclusion criteria: (1) patients aged > 19 years; (2) functional ovarian cysts that regress following a hormonal treatment; (3) lack of the signed informed consent.

Ovarian tumors were classified according to the WHO classification criteria (2014) and staged according to the FIGO classification (2013) [5].

The rAFS classification was used *to assess the severity of endometriosis*: grade I - 1-5 points, grade II - 6-15 points, grade III - 16-40 points, and grade IV - >40 points [10].

The World Society for Abdominal Compartment Syndrome (2006) was used *to assess the intra-abdominal pressure* (IAP) value, according to there are four grades of IAP level: gr. I - 12–15 mm Hg, gr. II - 16–20 mm Hg, gr. III - 21–25 mm Hg and gr. IV >25 mmHg.

For suspected prospective and retrospective versions of AT (external validation), the following scoring systems were used: (1) Compositional index according to King A. et al. (2014) [28]: nausea (no - 0, yes - 2); pain duration (>48 - 0, <48 - 2); ovarian volume (<20 ml - 0, 20–70 ml - 1, >70 ml - 2); ovarian rate (affected/unaffected) (<5–0, 5–10–1, >10–2); (2) composite index according to Schwartz B.I. et al. (2018); (3) the Bolli scoring (2017) - age (points = number of years) minus 3 points (if vomitus = "yes") and plus 1 point (if "pain duration >12 hours"). The optimal cut-off to classify patients with UAT or ovarian torsion was only 11.5 points [12,39].

Ovarian torsion is classified according to the following grades after Parelkar S.V. [11]: Grade 1 - slightly discolored, normal size, restores its color after detorsion; Grade 2 - dark red color changing into brown, a slightly enlarged ovary, which becomes hyperemic with multiple petechiae after detorsion; Grade 3 - brown color changing to black, the enlargement of the ovary followed by a developing hematoma, with a slight punctiform change in color after detorsion and hematoma evacuation; Grade 4 - completely black, with an obvious ovary enlargement, with a hematoma, which does not change color after detorsion and hematoma evacuation.

Characteristics of laboratory and instrumental research methods.

Clinical methods. The diagnosis of ovarian cyst or ovarian tumor was based on the patients' subjective data, such as complaints of pain in the hypogastric region of varying intensity, menstrual irregularities, an increase in the abdominal volume, dysuria. Objective findings included the presence of a palpable lesion in the pelvis. Additionally, laboratory methods for assessing the tumor markers and imaging methods of investigation were used to confirm the diagnosis.

***Laboratory methods*.** The patients included in the study underwent the following investigations: the assessment of the blood group according to the ABO/Rh system, complete blood count + platelets, a coagulogram, and the assessment of the lymphocyte-neutrophil index.

Tumor markers were assessed using the electrohemiluminescent method (eCLIA). The following values were considered as reference values: carbohydrate antigen - 125 – CA-125 (0-35 U/ml), carbohydrate antigen 19.9 or sialylated Lewis antigen – CA19.9 (0-39 U/ml), α-fetoprotein – AFP (0–5.8 IU/ml), carcinoembryonic antigen – CEA (0–4.7 ng/ml) by using Siemens Immulite 2000 xp (Germany).

Imaging methods. Ultrasonography (USG) was performed mainly on Esaote MyLab 15, Sono Scape 8000 (China) and Toshiba Aplio 300 (Japan) devices using 3-5 MHz trans abdominal and 5-7.5 MHz transvaginal (rectal) transducers.

An ultrasound examination was carried out to assess the characteristics of cystic and tumor-like formations of the ovaries, as well as to assess the volume of both the affected ovary and the amount of the remaining ovarian tissue. The volume was calculated using the prolate ellipsoid formula (0.523×height×length×width). Ovarian lesion volume was analyzed independently of the remaining ovarian tissue in order to determine a possible association of the ovarian lesion volume with its malignancy. The volume of normal ovarian tissue was calculated by excluding the lesion amount and used to calculate the ratios between them. The volume ratio of the ovarian tissue was compared without considering the degree of ovarian lesion. The affected/unaffected ratio allowed to compare the ovarian tissue volume of the affected part, exclusive of the lesion, with the volume of the unaffected contralateral ovary. This was calculated by dividing the volume of the affected ovarian tissue by the volume of the contralateral unaffected ovary [14].

Ultrasonographic "morphological" index (UMI) was assessed according to the method described by Ueland FR., et al. (2003) and adapted by Jeoung HY., et al. (2008). UMI was calculated by summing up the points (0-5) obtained from the cystic mass volume and the points obtained (0-5) from their structure.

Spiral computed tomography (CT) was performed using SOMATOM Emotion Duo (Siemens, Germany), Siemens Somatom Sensation 64 (Siemens, Germany) and AquilionTM PRIME (Toshiba, Japan) CT scanners. This method allowed to assess the densitometric index (Hounsfield unit - HU) for the liquid and solid components of the ovarian masses.

Magnetic resonance imaging (MRI) was performed using 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 following criteria were used to evaluate the size of the ovarian cystic and tumor-like masses: "giant" > 15 cm after Ye LY.: "large" > 8 cm in adolescent patients and > 5 cm in pubertal patients according to Amies Oelschlager AM. [4].

Information content of the radiological methods of investigation in the diagnosis of ovarian cysts and tumors in both retrospective and prospective studies was assessed by calculating the following parameters: Sensitivity (Se) = a/(a+c) and Specificity (Sp) = q/(b+q). The Cohen's kappa index was used to assess the reliability of the radiological methods at values of 0.01–0.20 (slight agreement), 0.21–0.40 (medium agreement), 0.41–0.60 (moderate agreement), 0 .61–0.80 (substantial agreement) and 0.81–1.00 (full agreement).

Laparoscopic surgeries for cystic and ovarian tumors were performed using the MGB (Germany) and Richard Wolf GmbH (Germany) video laparoscopes.

Morphological methods were performed within the Department of Morphopathology of IMPH IM and C. Anatomical and surgical tissue sampling was used as a material for morphological studies. The samples were previously fixed in a 10% formalin solution for 6-12 hours, then processed according to standard histomorphology protocol using the TISPE® ultra (DiaPath, Italy) ultravacuum histoprocessor and Raffaello® (DiaPath, Italia) automated staining network of section-based histomorphological tests with 3-4μ thickness made at the microtome "SLEE MANIS-CUT 6062". The classic *hematoxylin-eosin* (H&E) and mucoprotein-mucin

selective method using the Alcian-blue (methylene blue) dye was used in the staining step. Histological examination was performed by using microscopes: Nikon Labophot-2 and Calr Zeiss on the ×10 eyepiece and ×2.5 lenses; ×10; ×20; ×40. Images - Canon PowerShot A1000IS, captured in JPEG format.

Immunohistochemical methods were performed on deparaffinized sections, 4 μm thick. As an exposure method, heating of the sections of the vial with Tris buffer in a water bath (t=97°C for 40 min) was used. Endogenous peroxidase was blocked by incubating the sections in 3% hydrogen peroxide (15 min). Immunohistochemical reactions were visualized using the Envision FLEX high pH reagent kit (Dako, Denmark). The sections were stained with hematoxylin. Positive controls for each antibody were selected according to the manufacturer's specifications:

- to assess the **cytokeratin 7 (CK-7)** expression - mouse monoclonal antibodies (1:50 dilution, clones OV – TL 12/30, DAKO®, Denmark);
- anti-human mouse monoclonal antibodies to **cytokeratin 20 - CK-20** (1:25, Monoclonal Mouse Anti Human cytokeratin 20 antigen, Ks20.8 clones, Dako®, Denmark).
- anti-human mouse monoclonal antibodies for **carcinoembryonic antigen - CEA** (Monoclonal Mouse Anti Human carcinoembryonic antigen, Ready-to-Use, clones II-7, Dako®, Denmark);
- mouse monoclonal antibodies (clones 8A9, DAKO®, Denmark) were used to assess **placental alkaline phosphatase (PLAP)**;
- mouse monoclonal antibodies (Clone MIB-1, Dako®, Denmark) were used to determine **Ki-67** expression;

Immunohistochemical expression in the cytoplasm and cell membrane was assessed by the following intensity - Cy+, M+ (poor expression); Cy++, M++ (moderate expression) and Cy+++, M++++ (intense expression).

The study of tooth-forming elements in mature ovarian teratomas was carried out by ***scanning electron microscopy*** using a VEGA TESCAN TS 5130MM device (Czech Republic), followed by a radiospectral study of the solid component (tooth-forming component) by dispersive X-ray spectroscopy using energy-dispersive equipment Oxford Instruments x-beam system (Great Britain). This investigation was carried out on the basis of the National Center for Materials Study and Testing (NCMST) within the Technical University of Moldova.

Statistical processing of quantitative values was carried out via the analysis of variations. Arithmetic mean (M), mean error (m), and confidence interval (95% CI) were calculated. The Kolmogorov-Smirnov test was used to determine the normality of the data distribution. In case of normal sample distribution, the significance of the difference between the means was assessed using the Student's t test (t). In case of a significant deviation from normal sample distribution, the Mann-Whitney U-test was applied. When comparing the indicators of the three groups, the ANOVA test was used. Fisher's exact test was applied to compare relative values. The results were considered statistically significant at $p < 0.05$. The information content measurement in UAT was carried out by comparing ROC (Receiver Operating Characteristic) curves. The test information content was assessed as excellent (AUC>0.9), very good (AUC=0.81–0.9), good (AUC=0.71–0.8), satisfactory (AUC=0.61–0. 7) and unsatisfactory (AUC=0.6).

The prediction of OC and OT recurrences after the surgical treatment in the late postoperative period was performed using the Kaplan – Meier method using the log – rank test (Mantel-Cox). Statistical processing was performed using Graph Pad Prism 5.0 software (Graph Pad Software, Inc.).

3. DIAGNOSTIC PECULIARITIES OF OVARIAN CYSTS AND TUMORS IN CHILDREN AND ADOLESCENTS

3.1. Imaging features of cystic ovarian and tumor masses in children and adolescents

Within the framework of this study, ultrasound was performed in all cases, while transabdominal ultrasound was used in 176(65.9%) cases and transvaginal ultrasound was used in 91 (34.1%) cases. CT/MRI was carried out in 21(7.9%) patients, the indications being: (1) the presence of a solid component in the ovarian mass; (2) suspicion of tumor malignancy; (3) bulky tumor size; and (4) the inability to determine the nature of the abdominal cystic/tumor masses. Large ovarian masses (> 8 cm) were found in 120(44.9%) cases, and giant ones (> 15 cm) in 22 (8.3%) cases [4]. The distribution of ovarian mass characteristics in OC and OT is presented in table 1.

Table 1. Distribution of the radiological pattern of OC and OT in pediatric patients (n=298)

Radiological pattern	OC/OT, with no complications	OC/OT with complications	Total
Cystic	204(68.4%)	25(8.4%)	229(76.8%)
Combined (cystic/solid)	45(15.1%)	12(4%)	57(19.1%)
Solid	11(3.7%)	1(0.4%)	12(4.1%)
Total	260(87.2%)	38(12.8%)	**298(100%)**

Note: OC –ovarian cyst, OT –ovarian tumor

Ovarian serous cystadenoma (SCA) was found in 36(27.3%) cases of the total number of patients with OC. When performing USG and Doppler velocimetry with the transabdominal transducer - 22(61.1%) and transvaginal - 14(38.9%), SCAs presented as unilocular formations mobile or slightly mobile, of a regular spherical shape, externally outlined and a regular internal surface (Figure 1). The mean thickness of the SCA capsule was 5.9±0.3 mm, the cystic mass content characterized as anechoic.

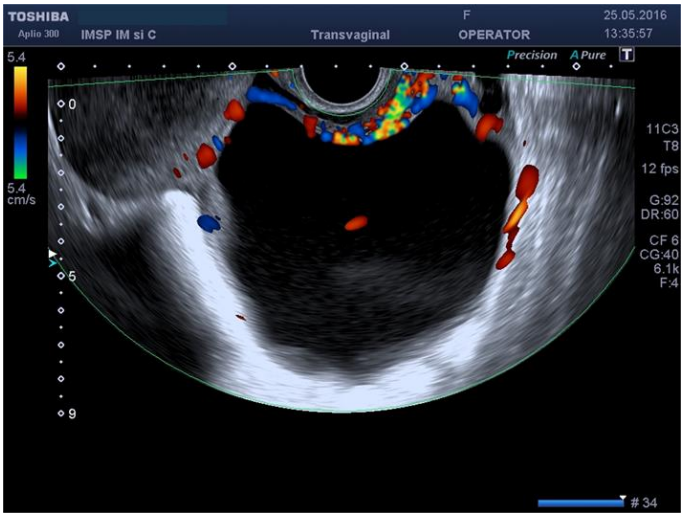

Figure 1. Transvaginal ultrasonography with Doppler velocimetry: SCA of the right ovary 111x96 mm

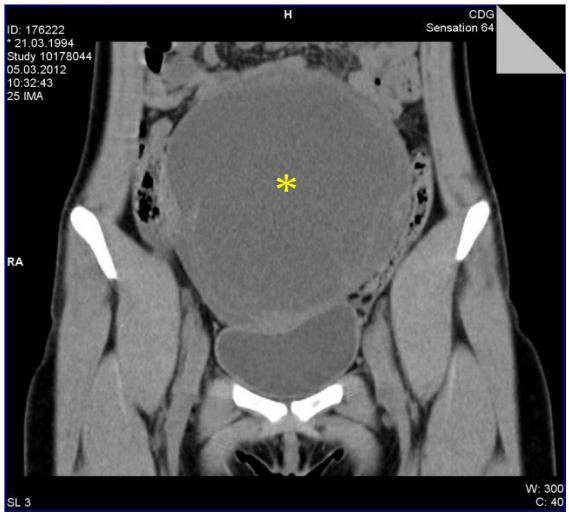

Figure 2. Computed tomography: giant ovarian serous cystadenoma (158x1381x14 mm) of the right ovary (*)

In 20(52.6%) cases, SCA was regarded as large and in 8(21.1%) as giant ones. The ultrasonographic "morphological" index averaged 3.9±0.2 (from 2 to 5). In 33(86.8%) cases of Doppler ultrasound images, vascularized structures were determined in the SCA capsule. CT was performed in 2(5.4%) patients. These types of ovarian tumors were visualized as unilocular, giant ovarian masses with or without intratumoral septa, with a density of 19–21 HU and a 9-10 mm thick capsule (Figure 2). According to MRI data (n=3), SCAs wererecorded as giant unilocular cystic mass with a clear contour and liquid content.

Ovarian mucinous cystadenoma (OMC) was diagnosed in 15 (10.9%) cases and accounted for 20% of the OET structure. According to USG and Doppler velocimetry data, OMCs were characterized by the following radiological structures: (1) regular-shaped masses (round, oval); (2) smooth or uneven outer contour; (3) multilocular formation with multiple septa of different thickness; (4) contents with echogenic suspension; (5) capsule of different thickness; (6) presence of blood flow in the capsule and septa (Fig. 3). In 7(46.7%) cases of OMCs, they were classified as large and in 3(18.8%) as giant ovarian masses.

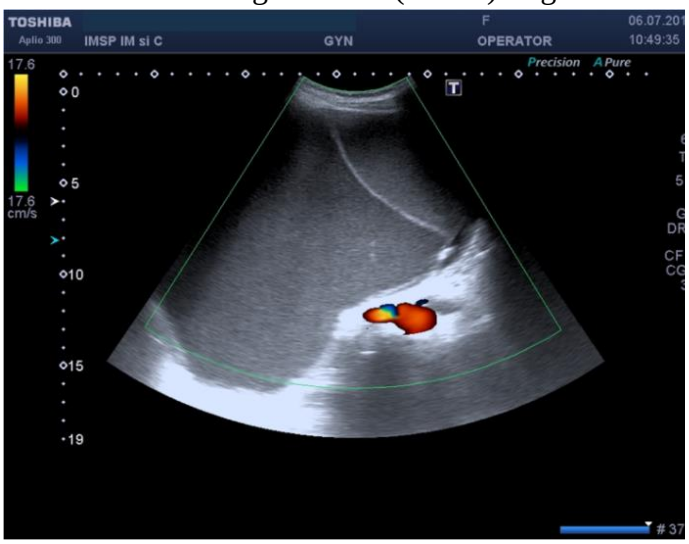

Figure 3. USG: giant, multilocular mucinous cystadenoma of the right ovary

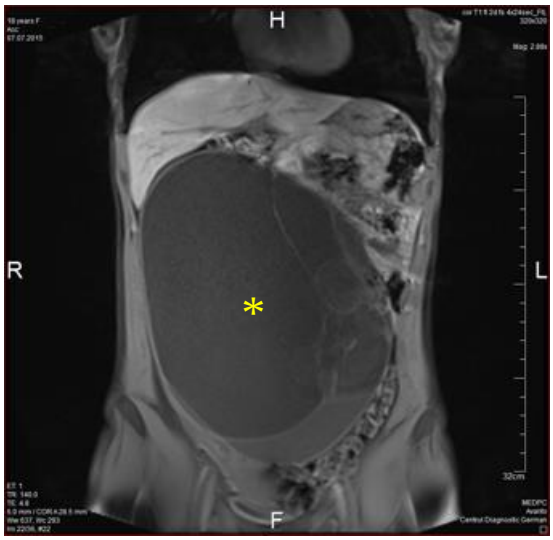

Figure 4. MRI (T1W, frontal plane): giant mucinous cystadenoma (*) of the right ovary

On MRI (n=1), OMC were visualized as multilocular cystic masses, with a regular outer contour, liquid content, non-homogeneous with a heterogeneous signal in T1W , with 1-3 mm thick septa (Figure 4). Comparing the ultrasound parameters in OMC and SCA, it was found that type 1 OET is larger in terms of maximum tumor size ($p=0.0862$) and tumor volume ($p<0.05$), as well as based on the USG “morphological” index ($p<0.0001$).

Papillary ovarian cystadenoma (PpOC) was found in 6(4.3%) cases and accounted for 8% of the OET structure. The following ultrasound features are characteristic of POC: (1) the presence of single or multiple papillary components, typically of 2-4 mm; (2) PpOC content is commonly non-echogenic; (3) blood flow in most cases was determined in the tumor capsule and papillary component (Figure 5 a, b).

The mean PpOC volume was 264.9±113.9 cm^3 (from 42.5 to 789.9), and the USG "morphological" index was 5.5±0.5 (from 4 to 7). The CT exam (n=2) revealed POC as cystic, homogeneous, liquid masses with a density of 19-21 HU, well-defined contour, with ≈ 5 mm thick capsule, with no enhancement after contrast intake.

Ovarian endometriomas (OE) accounted for 16% of the OET structure. According to ultrasound data, OE is characterized as a well-defined mass, with opaque content, regular

internal contour, poorly vascularized, sometimes with parietal ecodense component, nonvascularized.

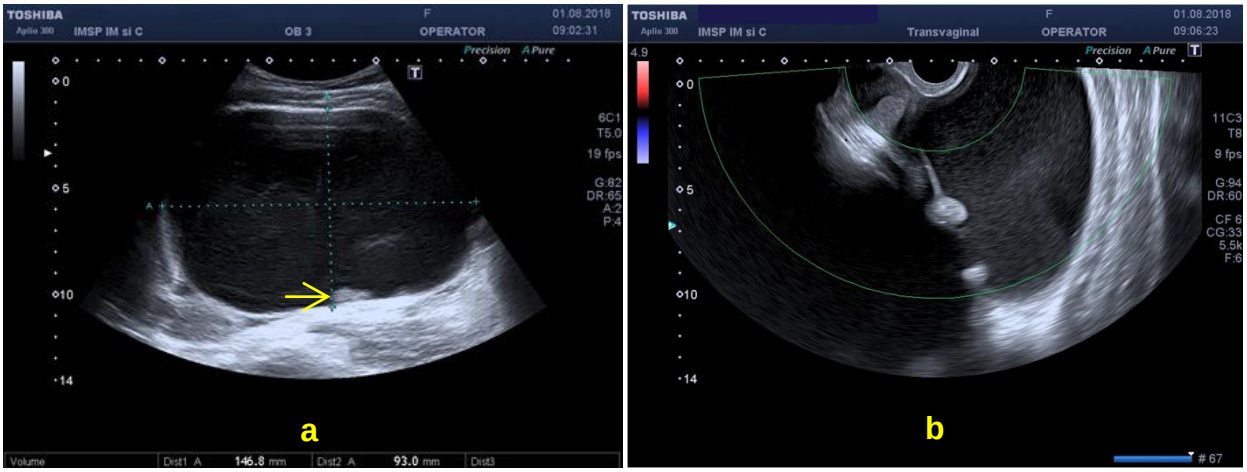

Figure 5 (a, b). Transvaginal USG with Dopplerography (P.D., 17 years): POC of the left ovary (146x109x93 mm), single papillary growths (→)

Mature ovarian/cystic teratoma (MCT) or dermoid was recorded in 52(39.4%) cases of the total number of patients with OT. On ultrasound, MCTs ranged from cystic masses with a solid peripheral node (Rokitansky node) to a partially echogenic formation with acoustic sound attenuation due to content of fat, calcium fragments, and multiple echogenic echoes owing to the hair elements within the tumor cavity (Figure 6).

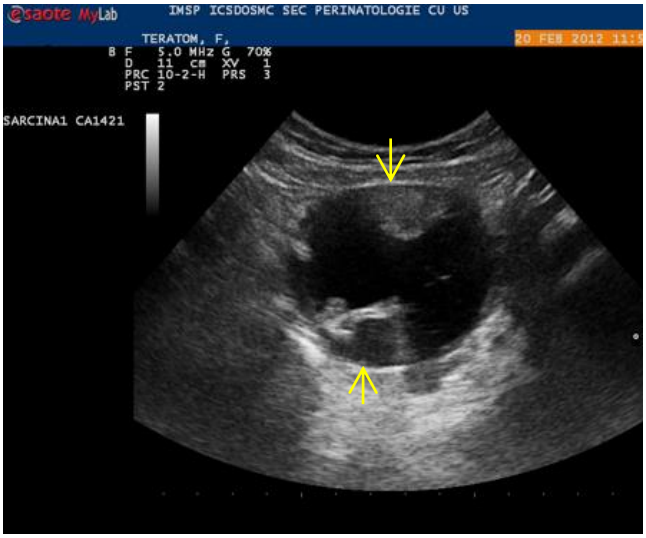

Figure 6. Ultrasound: mature teratoma of the left ovary, Rokitansky node (→)

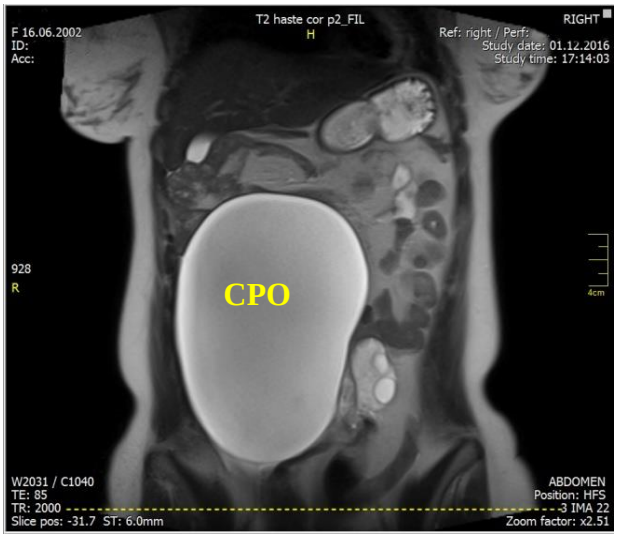

Figure 7. MRI T2W: Giant left POC (20x15x8.5 cm) extending to the right side of the abdomen

On CT scan (n=1), MCT was visualized as a mixed formation containing a liquid component (density ≈13-14 H.U.), fat (112 H.U.), including the tooth-forming elements (989 H.U.). MRI (n=1) revealed the following characteristic features of MCT: high signal intensity to the fat component, low signal intensity in soft-tissue protuberances (Rokitansky nodules).

Stromal OTs (fibroma, tecoma, fibrotecoma) were found in 3 cases, accounting for 2.9% of the total number of OTs in pediatric patients. On ultrasound, SOTs were visualized as solid, oval (n=3) or round (n=1) masses with a regular and smooth contour. Mean ultrasonographic "morphological" index scored 7.7±0.9. When assessing the echogenicity of the tumors, most

registered tumors were hypoechoic (n=3) and one case showed a mixed echogenicity (n=1). Doppler mapping assessment revealed minimal blood flow.

On the basis of X-ray methods of investigation, data for ***ovarian malignancies (MOT)*** were detected in 3(2.3%) cases preoperatively, and the diagnosis was confirmed by subsequent morphopathological and immunohistochemical studies.

The main signs of MOTs were as following: giant size OT – granular cell tumor, Sertoli-Leydig or large size – dysgerminoma; the presence of a solid component – Sertoli-Leydig granular cell tumor or dysgerminoma, a solid OT.

Follicular ovarian cysts (FOCs) were detected in 81(50.6%) cases out of the total number of OCs. FOCs were visualized as transonic masses with a regular internal contour, welldefined, poorly vascularized peripherally. The mean volume was 206.1±22.6 cm^3 (95% CI:160.8-251.2). The assessment of the ultrasonographic "morphological" index in FOCs registered a structural score was zero in all cases, whereas the total score was 3.1±0.1 (from 1 to 5).

Simple (serous) ovarian cyst SSOC was detected in 18(11.3%) cases of pediatric patients with OC included in the study. On US, SSOC were visualized as hypoechoic masses with thin walls and liquid content. SSOC cases were classified as large in 6(33.3%) patients and giant in 1 (5.6%) child. The ultrasonographic "morphological" index was 2.9±0.2 (1 to 5) in all SSOC cases, mostly in terms of volume, and structurally was equal to zero.

Paraovarian cysts (POCs) were recorded in 51(19.1%) of the total number of cysts. POCs were visualized as spherical or ovoid masses with thin walls, with homogeneous and non-echoic content separated from ipsilateral ovary (Figure 7). Only one POC case was found to exhibit a non-homogeneous content mass with non-vascularized parietal vegetation on a wide insertion base up to 38 mm. In all cases, Doppler sonography did not determine the blood flow in POCs. An accurate preoperative diagnosis was made in 29(56.9%) cases. The mean values of the ultrasonographic "morphological" index were - 3.5±0.2 (from 1 to 7) and the structural score was *zero* in 98.1% of cases.

Summing up this subchapter, it is worth mentioning that diagnostic imaging methods allow: (1) to almost accurately stratify cystic and tumor ovarian masses in children (benign and malignant); (2) to determine the optimal surgical approach (laparotomy *vs.* laparoscopy); (3) to choose the laparotomic approach (Phannenstiel incision *vs.* midline incision); (4) to plan the surgery volume (cystectomy *vs.*oophorectomy). The inclusion of CT and MRI in the algorithmic approach for diagnosing ovarian masses in children and adolescents makes it possible to increase the number of ovarian surgeries, a fact confirmed by other similar studies [14].

The inclusion of CT and MRI in the diagnostic algorithm of ovarian tumor-like masses in children and adolescents allows to increase the number of ovary-preserving surgeries, a fact established in other analogous studies [14].

3.2. The role of tumor markers in ovarian cystic and tumor masses in children and adolescents

Assessment of the level of tumor markers in ovarian tumors in pediatric patients is mandatory to distinguish between benign and malignant ovarian tumors, which might impact the volume of surgical intervention [18, 20]. The serological level of the CA-125 tumor marker was determined in 69(25.8%) patients included within this study. In 6(9.4%) cases of all patients tested with BOT (n=64) an increase in CA-125 level (from 37.1 to 104.5 U/ml) was registered and the results were interpreted as false positive. As regarding the MOT, only one patient

showed an increase in the CA-125(96.7 U/ml) tumor marker in the Sertoli-Leydig tumor, whereas in other cases (80%), the results were interpreted as false negative (from 16.9 to 34.5 U/ml).

The *AFP* marker was evaluated in 37(13.9%) cases. An increase in AFP serological concentration was found in one patient (2.7%) with secondary MOC that had a low malignant potential and in one patient (3.03%) with OMC. False negative results were reported in three of the four cases (75%) in MOT.

The level of the CA-19-9 tumor marker was determined in 43(16.1%) cases. An increase in the serological level of CA-19-9 was found in 3(6.9%) cases from the MCT group only, the values ranging from 41.5 to 54.2 U/ml. The CEA was determined in 42(15.7%) patients with OC and OT, showing normal data in all the cases. While summing up this chapter, it should be noted that: (1) currently, there is no single and universal tumor marker for preoperative stratification of OT in children and adolescents, as well as for determining the volume of surgery; (2) only a wide range of tumor markers (AFP, β-hCG, CA 125, LGD, CEA and CA 19.9) in combination with radiological imaging data (ultrasound, CT, MRI) provide the best approach in the differential diagnosis of BOT and MOT in children; (3) the serological level of tumor markers alone cannot be considered as a final decision-making factor in the treatment of children with ovarian tumors.

3.3. Clinical, laboratory and radiological characteristics in uterine adnexal torsion

ATs were detected in 36(13.5%) cases within this study. The major clinical symptom reported in all AT cases was the sudden onset of pelvic pain of a varying intensity. The assessment of the pain syndrome was carried out via the Wong-Baker FACES Pain Rating Scale (2009), the mean score ranging between 6.1±0.3 (1 to10). On abdominal palpation, all the patients complained of local pain of a varying intensity, whereas in 10(27.8%) cases, there were bulky masses in the abdominal cavity that were painful to the touch. The mean values of NLR in AT were three times higher than in the group without this complication (Figure 8). The NLR values were 3 or higher in 28(77.8%) cases from the AT group.

When analyzing this index, depending on the disease duration, it was found that in cases where the duration of the disease <24 hours, the NLR was higher compared to that of > 24 hours - 5.3±0.6 *vs.* 3.6±0.3. When comparing the NLR value and the level of ovarian ischemia, a statistically significant difference in indicators was found, thus, grade I - 2.3±0.2 *vs.*grade II – 4.5±0.8 *vs.* grade III - 4.3±0.7 *vs*. grade IV - 5.3±0.5 (p=0.0498, ANOVA test).

A similar dependence was observed in the NLR assessment, depending on the AT degree: single (180°) - 2.3±0.2 *vs.* double (360°) - 4.2±0.6 *vs.* triple (540°) - 4.7±0.5 *vs.* quadruple (720°) - 6.1±0.9 (p=0.0021, ANOVA test). The assessment of the informative NLR value in the diagnosis of UT based on ROC, a rather high value of the ROC curve/AUROC>0.9 was found and recognized as being excellent (Figure 9).

USG was applied in all pediatric patients (n=36, 100%) with UT, as a diagnostic method, including transabdominal (n=28, 77.8%) and transvaginal (n=8, 22.2%) imaging. A bulky ovarian torsion was found in AT with a mean volume of 275.1±36.3cm^3 (95% CI:201.4–348.9). On imaging, the ovary was described as hypoechoic, with edematous stroma (n=31, 86.1%) and peripheral follicles (n=17, 47.2%), which are pathognomonic radiological signs for AT [13, 21].

Doppler velocimetry (n=17, 47.2%) revealed no blood flow in 12(70.5%) cases, including a lack of venous blood flow and the presence of arterial blood flow in 8(66.7%) cases, as well as the lack of both venous and arterial blood flow in 4(33.3%) patients.

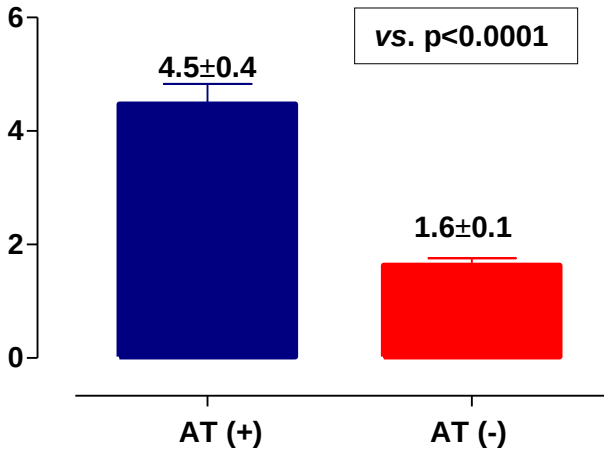

Figure 8. NLR values in presence (AT +) and absence (AT-)

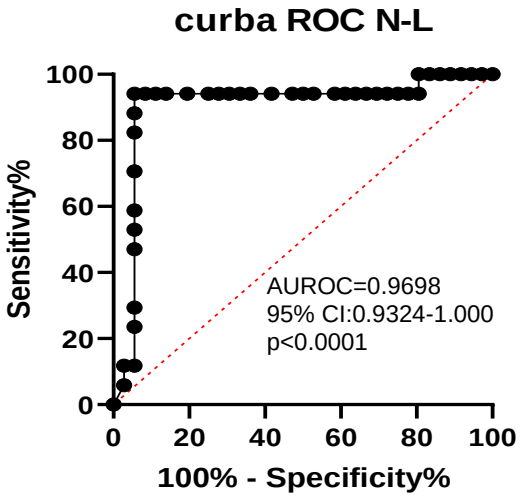

Figure 9. ROC curve for NLR

The external validation of the compositional index after King A. et al., 2014 (CIK) [16] showed that there was a statistically significantly higher scoring in the group with AT compared to the group without AT (Figure 10).

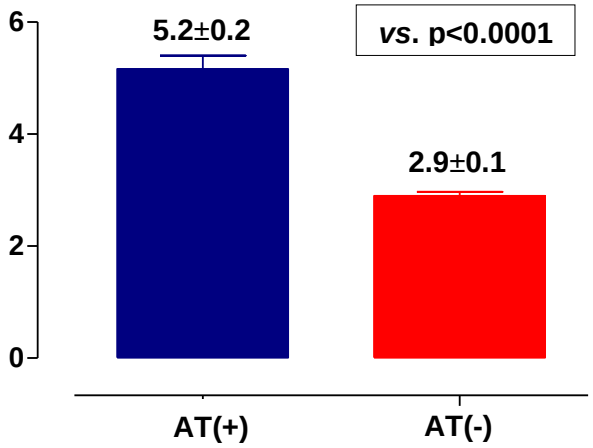

Figure 10. Scoring after CIK in presence and absence of torsion (AT +) and (AT-)

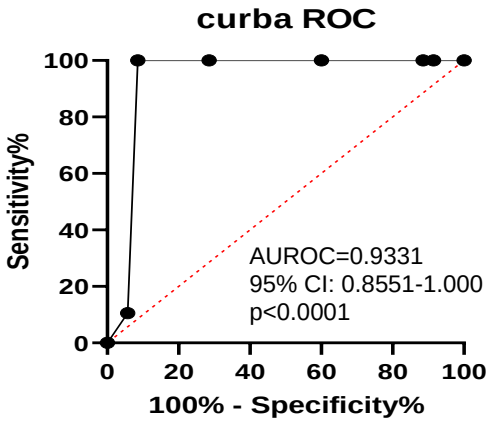

Figure 11. ROC curve for CIK

The informative value of CIK in the diagnosis of AT relates to the excellent category (AUROC> 0.9) based on the ROC curves (Figure11). The CIK value does not depend on the duration of the disease (<24 hours *vs.* >24 hours), the value having 5.2±0.3 *vs.* 5.1±0.2 (p>0.05) within these time intervals. Moreover, it also does not depend on the ischemia level, the indices being for gr. I. - 4.8±0.9 *vs.* gr. II - 4.8±0.7 *vs.* gr.III - 5.4±0.4 *vs.* gr. IV- 5.3±0.2 (p=0.9045, ANOVA test), as well as on the torsion level, being unique (180°) - 4.8±0.9 *vs.* double (360°) - 5.1±0.4 *vs.* triple (540°) - 5.4±0.4 *vs.* quadruple (720°) - 5.1±0.2 (p=0.9260, ANOVA test). Another useful tool applied in this study is the scoring system according to Bolli P., which stated the principle "the lower the scoring, the more likely AT is present" [7]. When assessing the

information content of this scoring system in the diagnosis of AT, the AUROC indicator ranged between 0.71-0.8, the result corresponding to the "good" category. The analysis of the Bolli P. scoring points, depending on the duration of the disease (<24 hours *vs.* >24 hours), showed no significant difference in groups. Summing up the data on validation of scoring systems in AT, it should be noted that composite indices showed the best results, and included clinical and ultrasound data.

4. EARLY AND REMOTE RESULTS OF SURGICAL TREATMENT OF OVARIAN MASSES IN CHILDREN AND ADOLESCENTS

4.1. Peculiarities of surgical treatment of ovarian cysts and tumors in children and adolescents

Surgical treatment is the method of choice in the treatment of ovarian tumors (OT) and symptomatic ovarian cysts (OC). Despite the successful results obtained in the preoperative examination by using radiological methods and tumor markers, as well as the advance of surgical techniques, the frequency of ovariectomies (salpingoovariectomy) in benign ovarian tumors is quite high and ranges from 15 to 58% [19].

Table 2. The volume of surgical intervention in uncomplicated cystic and tumor formations of the ovaries (n=258)

Volume of surgical intervention	Nature of ovarian masses		
	OC (n=143)	BOT (n=107)	MOT and BLOT (n=8)
cyst (tumor)ectomy	133(93%)	87(81.3%)	4(50%)
cyst(tumor)ectomy+ovarian resection	3(2.1%%)	1(0.9%)	-
cyst(tumor) ectomy + tubectomy	2(1.4%)	-	1(12.5%)
ovariectomy	2(1.4%)	6(5.6%)	1(12.5%)
salpingoovariectomy	3(2.1%)	13(12.2%)	2(25%)

Note: OC – ovarian cysts, BOT – benign ovarian tumors, MOT – malignant ovarian tumors, BLOT – borderline ovarian tumors

This study was conducted on 267 pediatric patients with ovarian masses (n=296) who underwent a surgical treatment for OCs in 158(53.4%) of total cases and for OTs in 138(46.6%) cases. In 229(85.8%) patients the surgeries were performed for uncomplicated OC and OT, and in 38(14.2%) - for intraabdominal complications: AT (n=36), spontaneous rupture (n=2). Laparotomy was the surgical approach performed in 181(67.8%) patients, Phannenstiel laparotomy in 174(96.1%) and median laparotomy in 7(3.9%) cases. The distribution of surgical methods used in uncomplicated OCs and OTs is presented in Table 2. Of the total number of OC and OT, ovary-preserving surgeries were performed in 231(89.5%) cases, and (salpingo)ovariectomies in 27(10.4%) patients. The technical aspects of the perfect cyst (tumor)ectomy followed by an optimal preservation of ovarian tissue in pediatric patients were registered in the rationalization proposal no. 392, of 12.05.2014 (IMPH IMC). An appropriate dissection plan allows: (1) to preserve the integrity of the cyst (tumor); (2) to enucleate the ovarian mass without volume reduction of the remaining ovarian tissue with minimal blood loss. The rationality of using these principles in ovarian cystectomy has also been described in other similar studies [2].

In the group of *mature cystic teratoma* (MCT) (n=52) in 46(88.5%) cases the surgeries were performed by Phannenstiel minilaparotomy and in 6(11.5%) patients laparoscopic technologies were used. It should be noted that OE(SOE), in uncomplicated MCTs, was performed more often at the initial stages of the study, the ovarian-sparing surgeries accounting for only 72.2% cases, and from 2006 until the end of the material collection, these surgeries were carried out in all cases (24/24,100%).

There were two surgery choices in the group of *ovarian epithelial tumors* (OET) (n=72), viz. laparotomy (n=47,65.3%) and laparoscopy (n=25,34.7%). In 11(15.3%) cases, patients underwent immediate surgery due to AT. Most patients from the group with uncomplicated OET (n=41) underwent Phannenstiel laparotomy (n=37,90.2%), and 4(9.8%) patients had a median incision due to the large size of the tumor. Tumorectomies were performed more frequently in this statistical group ($p < 0.0001$) than OE(SOE), the ratio being 32(72.7%) *vs.* 12(27.3%). OMC was found in 17/132 (12.9%) cases included in this study and were presented in two variants: (1) cystic masses, unilateral large (> 8cm) (n=15) and (2) bilateral, solid, smaller than 8cm (n=2). This group underwent tumorectomy – 13/19(68.4%), salpingoovariectomy – 4/19(21.1%) and ovariectomy - 2/19(10.5%). The tactical aspects in mucinous ovarian tumors were registered for being rationalized based on proposal no. 448 of 06.02.2017 (Institute of Mother and Child).

Ovarian endometrioma (n=12,8.7%) was found in 11(8.3%) pediatric patients, including bilateral endometrioma in Mayer-Rokitansty-Küster-Hauser syndrome type I. Of the six cases of ovarian endometrioma operated on by laparotomy, tumorectomy was performed in most of the cases (n=5).

Fibromas/thecomas (n=4, 2.9%) were detected in 3(2.3%) children; in all cases, operations were performed by Phannenstiel minilaparotomy. In 2/4(50%), the dissection plan between the tumor and the ovarian tissue was determined quite clearly, which made it possible to perform an ovarian-sparing intervention.

Giant ovarian tumors are a fairly rare phenomenon and only unique cases are published in the literature [23]. Within the research framework, 14(10.6%) cases were diagnosed with giant masses of the total number of pediatric patients with OT (n=132). Phannenstiel laparotomy (n=7) and median incision (n=5) were used as a surgical approach, whereas in 2(14.3%) cases laparoscopic interventions were performed using the extracorporeal tumorectomy technique. Ovarian-sparing interventions was performed in 5(45.5%) patients from the group with giant ovarian tumors. The decision to perform ovary-preserving surgeries was made only if: (1) there was an adequate dissection plan between the tumor-like mass and the remaining ovarian tissue; (2) the possibility of dissection without compromising the integrity of the ovarian tumor and leaving tumor fragments on the remaining ovarian tissue. One of the most serious complications of giant ovarian tumors is the development of intraabdominal hypertension (IAH) syndrome and abdominal compartment syndrome (SHIA). In this study, IAH developed in 3/14(21.4%) cases of giant ovarian tumors.

The analysis of the surgical treatment peculiarities in OCs (n=158) in children and adolescents showed that ovary-sparing interventions was performed in 149(94.3%) cases, ovariectomies + salpingoovariectomies only in 9(5.7%) cases. Of the total number of patients with OC and OT, paraovarian cysts were found in 51(19.1%) patients or in 54/158(34.2%) of the total number of OCs. Depending on the surgical approach, all cases of POC were divided into two groups: I group –underwent surgery via Phannenstiel minilaparotomy (n=28, 54.9%) and II group –underwent minimally invasive operations using laparoscopic technologies (n=23,

45.1%). According to the volume of surgical intervention, the laparotomy approach was used in the first group (29 POC), and namely cystectomy (tumorectomy) - 24(82.8%), cystectomy + tubectomy - 3(10.4%), cystectomy + ovarian resection - 1(3.4 %) and salpingoovariectomy - 1(3.4%) were performed.

AT in children and adolescents is considered a complication of OC and OT, often leading to ovariectomy, which has been long considered the only treatment of choice for this disease [3, 10]. Out of 36(13.5%) cases of uterine adnexal torsion, 27(75%) patients underwent the traditional surgical method (laparotomy) and in 9(25%) cases laparoscopic technologies were used. As regarding the direction of the adnexal torsion, it was found that when summing up the both sides, medial torsion was more commonthan the lateral one, their frequency being of 31(86.1%) *vs*. 5(13.9%), respectively, which showed a statistically significant difference ($p<0.0001$). It should be noted that pronounced degrees of ovarian ischemia (III and IV degrees) occurred statistically true more often ($p<0.05$) than non-expressed ones (I and II degrees), accounting for 23(63.9%) *vs.* 13(36.1%), respectively.

Cyanotic ovaries occurred statistically true more frequently ($p=0.0020$) than "whitish" and necrotic ovaries, their ratio being of 25(69.4%) *vs.* 11(30.6%). The surgery performance in the AT group was based on tactics aimed at performing ovary-preserving surgeries by following the next steps: (1) assessing the torsion degree and severity of ovarian ischemia; (2) performing a staged detorsion (dosed tactics); (3) performing cyst(-tumor)-ectomy with ovarian reconstruction. The method of maximum reduction of I/R syndrome in ATs and performing ovarian cyst(-tumor)-ectomy operations with maximum preservation of ovarian tissue in pediatric patients was recorded in the rationalizing method no. 393 of 12.05.2014 (Institute of Mother and Child). Throughout the study, reconstructive maneuvers in AT were performed more frequently than ovary(salpingo-oophor)-ectomies, accounting for 22(61.1%) *vs.* 14(38.9%), respectively. While analyzing the frequency of ovarian surgery depending on the surgical approach, it was established that this index was 66.7% for laparotomies and 55.6% for laparoscopies. Chronologically considering, it should be mentioned that the development and implementation of the ovarian detorsion in ATs allowed to statistically significantly ($p=0.0054$) increase the number of reconstructive surgeries from 35.2% at the initial stage to 84.2% at the final stage.

4.2. Laparoscopic approach for cystic and tumor ovarian masses in pediatric patients

Within the study framework, 86(32.2%) laparoscopic interventions were performed in cases of OC and OT, by applying two surgical techniques: (1) laparoscopy with intracorporeal cyst-(tumor)-ectomies (n=63,73.3%) and (2) hybrid miniinvasive technologies – laparoscopically-assisted extracorporeal cyst- (tumor)-ectomies (n=23, 26.7%).

Laparoscopic interventions were indicated in OC (n=54, 62.8%) and benign OT (n=32, 37.2%). In 10(11.6%) cases, laparoscopic surgery was performed due to complications associated with the ovarian mass, including AT (n=9) and spontaneous rupture of the ovarian cyst in the free abdominal cavity (n=1).

The entire group of surgical intervention (LIC + LAEC) included as follows: cyst (-tumor)-ectomies - 86(94.5%), cyst (-tumor)-ectomies + tubectomy 1(1.1%) and salpingoovariectomy - 4 (4.4%). In 9(10.5%) cases, diathermocoagulation of the contralateral ovary was performed. When comparing the laparoscopic and open interventions, it was found that the frequency of ovary-preserving surgeries is statistically higher ($p<0.01$) when using minimally invasive

technologies. Moreover, the use of statistically significant laparoscopic technologies (p<0.0001) reduces the surgery timing, intraoperative blood loss, and hospital stay (Table 3).

Table 3. Comparative characteristics of traditional and minimally invasive approaches for OC/OT in children and adolescents

Parameters	**Laparotomy (n=181)**	**Laparoscopy (n=86)**	**Validity P**
Age (years)	16.1±0.1 (95% CI:15.78–16.41)	15.9±0.2 (95% CI:15.48–16.34)	p=0.4301*
BMI (kg/m^2)	21.8±0.2 (95% CI :21.31–22.22)	21.9±0.4 (95% CI:21.19–22.65)	p=0.9277*
OC/OT size (cm)	9.4±0.3 (95% CI:8.798–10.11)	8.3±0.4 (95% CI:7.560–9.045)	p=0.0338**
OSS	80.7%	95.6%	p=0.0013
Surgery timing (min.)	48.1±1.4 (95% CI:45.29–50.90)	29.5±1.1 (95% CI:27.32–31.82)	p<0.0001
Intraoperative bleeding (ml)	222.5±5.9 (95% CI:210.8–234.2)	65.2±3.4 (95% CI:58.30–72.03)	p<0.0001
Hospital stay (days)	6.6±0.2 (95% CI:6.183–6.928)	4.5±0.2 (95% CI:4.165–4.951)	p<0.0001

Note:*p>0.05 **p<0.05

Summing up this chapter it should be outlined that: (1) laparoscopic interventions using the standard endoscopic inventory (for adults) in children and adolescents with OC/OT seem to be technically feasible and safe; (2) laparoscopy is not a contraindication for benign ovarian tumors (including mature ovarian teratomas) and AT; (3) the LAEC method is rational to use for bulky and giant masses in pediatric patients; (4) while comparing laparotomy and laparoscopy, the latter is a priority confirmed by several cases of statistically true reconstructive operations on the ovary, shorter timing of interventions, reduced intraoperative hemorrhage and length of hospitalization.

4.3. Histopathological features and immunohistochemical profile of ovarian cystic and tumor masses in children and adolescents

Despite the successful advance of radiological methods of investigation, the conclusive diagnosis of ovarian cystic and tumor masses is possible only after a histopathological examination of the resected macroscopic samples, whereas some cases require an additional immunohistochemical study. Epithelial ovarian tumors were more common in the OT group - 76 (55.1%) cases, half of which were due to serous cystadenoma (SCA).

The second largest group of OET included the ovarianmucinous tumors (OMT), which were identified in 19(13.8%) of the total number of pediatric patients with OT. It should be noted that unilateral OMTs were more common than bilateral OMTs, accounting for 15(78.9%) *vs.* 4 (21.1%).Considering the hypothesis on the different origin of OMTs [9], the immunohistochemical profile was assessed by using monoclonal antibodies to cytokeratins (CK-7 and CK-20) and CEA.

Thus, for primary mucinous ovarian tumors, a positive expression of CK-7 (Figure 12) in the membrane (M ++/+++) and cytoplasm (Cy ++/+++) of epithelial cells, as well as a negative reaction to CA- 20 and CEA were registered. Low mitotic activity was found in the epithelium of

these ovarian tumors (Figure 13). For MOC, a pronounced cytoplasmic (Cy ++/+++) and membranous (M ++/+++) expression of both CK-20 (Figure 14) and CEA (Figure 15) was found, as well as a negative one for CK-7 in epithelial cells.

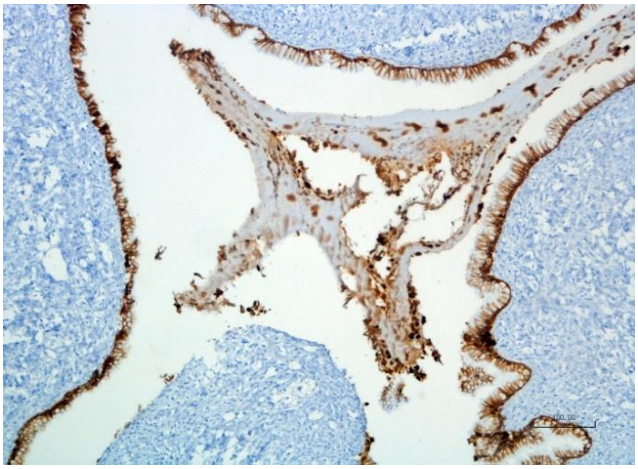

Figure 12. Immunohistochemistry: positive expression of CK-7 in OMC epithelium (DAB x100)

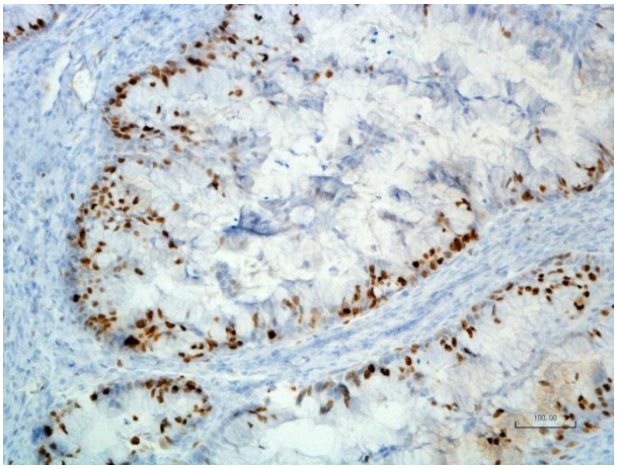

Figure 13. Immunohistochemistry: positive expression of Ki-67 in OMT epithelium (DAB x200)

The method of differential diagnosis between primary and secondary mucinous ovarian tumors by immunohistochemical study with the use of specific monoclonal antibodies was registered by a rationalizing proposal no. 443 of 10.02.2016 (IMPH IMC). This type of OMTs should be considered as metastatic tumors of low-grade appendiceal mucinous neoplasms and can potentially be associated with the development of pseudomyxomaperitonei.

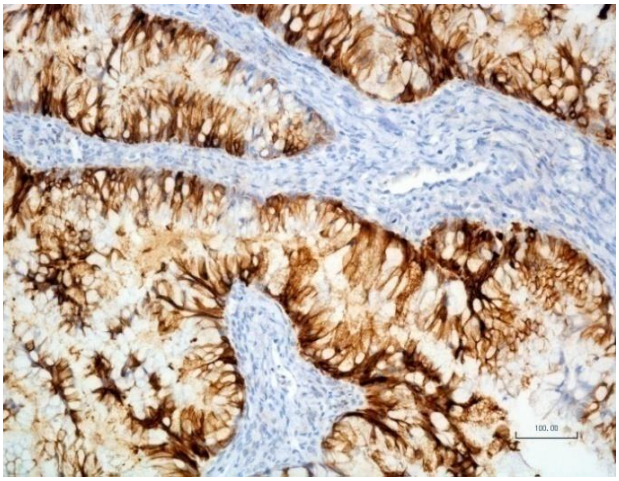

Figure 14. Positive CK-20 expression in the secondary OMTepithelium (DAB x200)

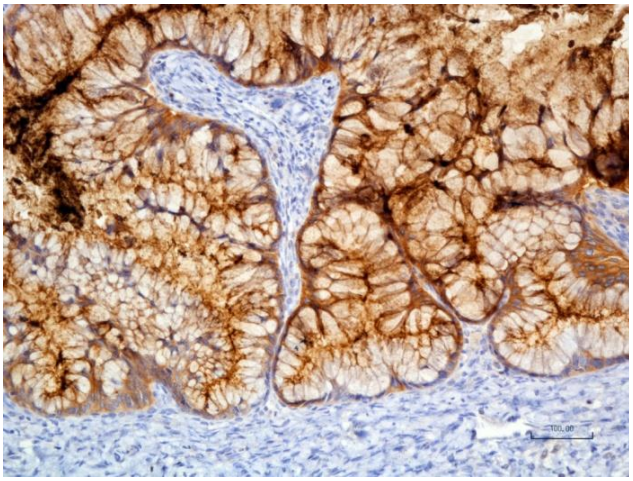

Figure 15. Immunohistochemistry: positive expression of CEA in the secondary OMT epithelium (DAB x200)

The next subgroup of ovarian epithelial tumors comprised the ovarian endometriomas, which were identified in 12(8.7%) cases of the total number of ovarian tumors in children and adolescents. A fairlyrare group of OETs in pediatric patients are the papillary ovarian cystadenomas, which occurred in 6(4.3%) of the total number of ovarian tumors in children and adolescents. Ovarian cystadenofibroma was the least common epithelial ovarian tumor, which was detected in only one case (0.7%) within this study.

The liquid component of MCT was characterized as mucinous (gelatinous) - 27(51.9%), serous - 12(23.1%), semi-transparent serous - 7(13.5%) and hemorrhagic - 6(11.5%). The

structure of the solid macroscopic sampling of MCT included: hair (n=51, 98.1%), curd material (n=49, 94.2%) and osteogenic and tooth-forming elements - 7(13.5%). The histological examinations revealed the structural basis of MCT characterized by micro-macrocystic structures and relatively solid plateaus consisting of various mature tissues, which are derivatives of the three embryonic layers: ectoderm, mesoderm and endoderm. The type of tissues and the frequency of their occurrence depending on the embryonic layer in MCTs are shown in Table 4.

Table 4. The types of morphological tissues in MCT

Embryo layer type	Tissue derivatives	N	%
Ectodermal tissues (∑=128)	scaly epithelium	41	78.8
	keratin	33	63.5
	skin with skin attachments	29	55.8
	neuronal	23	44.2
	choroidal epithelium	1	1.9
	transient epithelium	1	1.9
Mesodermal tissues (∑=156)	vascular (blood/lymph)	52	100
	fibrofatty tissue	52	100
	lymphatic	12	23.1
	smooth muscle	12	23.1
	myxoid	9	17.3
	teeth	8	15.4
	osteogenic	5	9.6
	osteocartilaginous	2	3.8
	hematopoietic	2	3.8
	skeletal muscles	2	3.8
Endodermal tissues (∑=52)	cystic glandular clusters	38	73.1
	glandular thyroid	6	11.5
	respiratory epithelium	6	11.5
	epithelium / gastrointestinal mucosa	2	3.8

Based on the OT incidence in children and adolescents, germinogenic tumors (n=53, 38.4%) ranked second among all the cases and included two variants: the mature ovarian teratoma (MCT) and the monodermal teratoma (epidermoid) which accounted for 52(37.7%) *vs.* 1(0.7%), respectively.

Stromal tumors were diagnosed in 4(2.9%) of the total number of ovarian neoplasms in pediatric patients. In all cases, these tumors were characterized as solid masses of white-yellow color on section. Of the total number of OTs (n=138), malignancies were detected in only 3(2.2%) cases, including granular cell tumors (n=1), Sertoli-Leydig cell tumors (n=1), and dysgerminoma (n=1).

The assessment of the morphological features of ovarian tumors in pediatric patients revealed benign ovarian masses in most cases (n=130, 94.2%). Malignancies, borderline tumors and secondary mucinous tumors with low-malignant potential accounted for only 8(5.8%) cases. The histological analysis of the ovarian cysts showed the following subcategories: follicular cysts (n=81, 50.6%), paraovarian cysts (n=53, 33.1%), serous (n=20, 12.5%), yellow body cyst (n=4, 2.5%) and parasitic cysts (echinococcus) (n=2, 1.3%).

4.4. Late outcomes of surgical treatment of ovarian cystic and tumor masses in children and adolescents

Within this research framework, a follow-up of late postoperative outcomes were followed in 205(76.8%) patients, of whom 170(82.9%) underwent OSS and 35(17.1%) – OE(SOE). The

group of patients who underwent OSS monitored within a remote postoperative period included OC (n=99) and BOT (n=71), whereas the mean length of surveillance was 71.1±3.3 months (95% CI: 64.51-77.60). The incidence of recurrent ovarian masses was 9(5.3%) cases, this index being lower in the OC group than in the BOT group, viz 4(4.1%) *vs.* 5(7.1%), respectively. Predicting OC and BOT recurrences after OSS via the unanimously accepted Kaplan – Meier method suggests a possible occurrence of ipsilateral ovarian formations ≈ in 16% of patients as late as 11 years after primary surgery.

The duration of recurrence after OSS was longer in the OC group than in the OT being - 30.1± 4.7 months *vs.* 17.1±2.8 months, respectively, while the difference was not significant (p=0.6228). The actual results obtained in the CO and TO recurrences following an OSS are fully corresponding to the data obtained via the Kaplan – Meier predicting method.

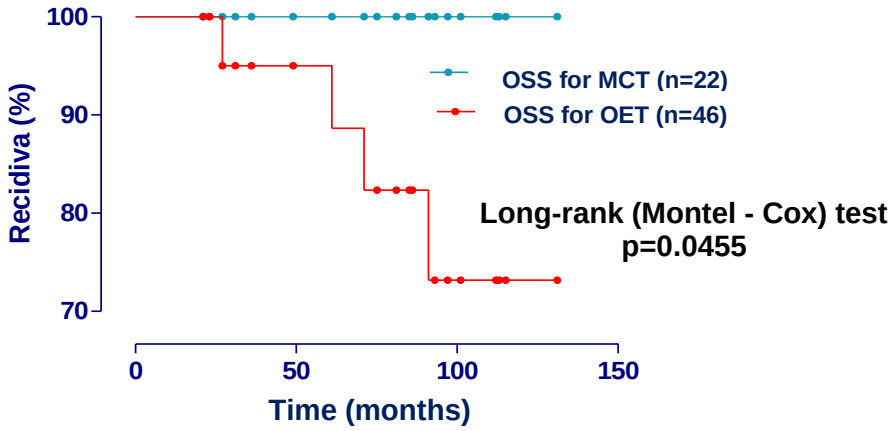

Figure 16. Prediction of BOT recurrence after OSS in MCT OET (Kaplan-Meier method)

OT recurrences were reported only in the group of patients with epithelial tumors (n=5, 10.8%) and were presented by OMT (n=3) and endometriomas (n=2). No recurrences were reported in the MCT group after OSS*(zero).* In predicting OT recurrences in these groups, a statistically true difference (p<0.05) was established in the DFS - disease free survival index (Figure 16). During this study, metachronous tumor formations in the contralateral ovary were registered in 21(10.2%) cases in the late postoperative period, over 28.7±3.9 months (95% CI:20.58-36.85).

GENERAL CONCLUSIONS

1. In most cases of CO and TO (88.8%), there were conclusive clinical manifestations (pelvic pain - 100%), increased abdominal volume (9.6%), urinary disorders (1.7%), on the contrary, at 11.2 % of children and adolescents, the pathology was evaluated asymptomatically, being detected incidentally at the USG examination (p <0.0001).
2. The results of the OMC ultrasound study exceed SCA both by the maximum diameter (p>0.05) and the volume (p <0.05) of the tumor, and by the ultrasonographic „morphological" index (p <0.0001). In the MCT stratification, classes B and C were mainly observed compared to A and D (p<0.0001). When comparing the frequency of occurrence of classes B and C, the differences proved to be at the limit (p = 0.006).

3. For stratification of OT according to additional imaging criteria, it is appropriate to use tumor markers, taking into account the false positive results recorded in the present study (for CA - 125 in 9.4%, CA 19-9 in 6.9% and AFP in 5.4%).
4. ATs was mainly characterized by medial rotation (86.1%) *vs.* (13.9%) of both sides, being rational to perform the dosed detorsion to level the I/R syndrome and the subsequent performance of ovarian-sparing operations cyst- (tumor)ectomy with maximum preservation of ovarian tissue, which influenced the significant increase in the rate of ovarian preservation from 35.2% to 84.2% of cases ($p = 0.0054$).
5. OT in children and adolescents were predominantly benign neoplasms (94.2%), of which epithelial (55.1%) and germinogenic (38.4%) ovarian neoplasms predominated. Secondary malignancies, borderline and mucinous tumors with low malignant potential accounted for 5.8% of cases. OMC is characterized by immunohistochemical profile - CK 7+/CK 20–/CEA– and CK 20+/CEA+/CK 7– for secondary OMC.

PRACTICAL RECOMMENDATIONS

1. The lack of a specific tumor marker for the preoperative stratification of OT in children and adolescents, and the determination of the volume of surgery dictate the need to observe the following principles: (1) the use of a wide panel of tumor markers (CA-125, AFP, β-hCG, LHD, CEA, CA 19.9); (2) tumor markers in combination with imaging data (USG, CT, MRI) for differential diagnosis of benign and malignant OT; and (3) the serological level of tumor markers cannot be considered a factor in the final decision on the volume of surgery.
2. The rationality of the use of CT and MRI in a preoperative diagnostic algorithm for OT in children and adolescents is due to the advantages of these methods and allows: (1) precise stratification of cystic and tumor formations of ovaries in children and adolescents - size, radiological pattern and the presence of the solid component (benign *vs.* malignant); (2) assessment of the method of surgery (laparotomy *vs.* laparoscopy); (3) choice of surgical approach (Pfannenstiel *vs.* median laparotomy); (4) planning the volume of surgery (cystectomy *vs.* ovarectomy).
3. Technically, the dissection stage of the cortical layer at the boundary between the tumor-like formation and the residual ovarian tissue is considered fundamental and allows: (1) not to violate the integrity of the cyst or OT (2) residual ovarian tissue with minimal blood loss.
4. Surgery for ATs in pediatric patients is initiated by dosing detorsion under visual control of restoration of ovarian blood flow, followed by ideal tumor-(cyst)ectomy, the reasoning being determined by: (1) the absence of complications after dosing detorsion; (2) low incidence of MOT in children and adolescents and (3) maximum maintenance of fertile function.
5. Performing laparoscopic interventions for cysts and OTs in children and adolescents requires compliance with the following principles: (1) feasible and safe use of standard endoscopic equipment (for adult patients); (2) maintaining the level of pneumoperitoneum at 8-10 mmHg for children and 10-15 mm Hg in adolescents; (3) Benign OTs (including MCTs) and ATs are not a contraindication for laparoscopic interventions; (4) for large and giant ovarian formations, the LAEC (*ex vivo*) technique is recommended; (5) clear evidence of the benefits for laparoscopic interventions *vs.* laparotomy, including a shorter duration of surgery, intraoperative bleeding, and length of hospital stay.

6. Surgery for OMC involves compliance with the following postulates: (1) prevention of externalization of the contents in the free abdominal cavity; (2) thorough debridement of the abdominal cavity and washing with 10% povidone iodine in case of externalization of the contents; (3) visual and palpable revision of the appendix; (4) completion of the appendicectomy intervention in the case of secondary OMC.
7. In case of secondary OMC, immunohistochemical studies are necessary to perform using monoclonal antibodies to determine the expression of cytokeratins (CK7, CK20) and CEA in tumor cells.

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- **Patents, registration certificates**

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29. Mișina A., Gudumac E., **Harea P.**Tumorile ovariene gigantice la copii și adolescente. Particularitățile diagnosticului radiologic, tratamentului chirurgical și caracteristicile morfologice. Seria O Nr.6592 din 26.05.2020

Distinctions
Diploma of gr. I for Poster Presentations with oral discussion

- At the VI Congress of the Society of Ultrasonography in Obstetrics and Gynecology (Bucharest, 2018);
- 1st International Congress of Gynecological Oncology (Bucharest, 2020).

Adnotare

Patricia Harea **″Diagnosticul și tratamentul chirurgical al formațiunilor chistice și tumorale ovariene la copii și adolescente″.** Teza pentru obținerea gradului științific dedoctor în științe medicale, Chișinău, 2022. Teza cuprinde introducere, 4 capitole, sinteza rezultatelor obţinute, concluzii generale, recomandări practice, 21 tabele, 133 figuri. Se atașează indicele bibliografic cu 295 surse. La tema tezei au fost publicate 27 de lucrări științifice.

Cuvintele-cheie:copii, adolescenți, chisturi ovariene, tumori benigne, maligne, tumori ovariene, torsiune ovariană, ischemia/reperfuzie, markerii tumorali, ultrasonografie, Doppler, tomografie computerizată, imagistica prin rezonanță magnetică, tratament chirurgical, chistectomie laparoscopică, chirurgia ovaromenajantă.

Domeniul de studiu: 321-15 – obstetrică și ginecologie

Scopul lucrării: Ameliorarea rezultatelor tratamentului chirurgical în formațiunile chistice și tumorale ovariene la copii și adolescente, în baza optimizării managementului diagnostico-curativ cît și a estimării rezultatelor tratamentului precoce și la distanță.

Obiectivele lucrării: (1) **s**tudierea particularităților manifestărilor clinice în formațiunile chistice și tumorale ovariene la copii și adolescente; (2) determinarea particularităților imagistice ale formațiunilor chistice și tumorale ale ovarelor la pacientele pediatrice; (3)aprecierea informativității markerilor tumorali în diagnosticul formațiunilor tumorale ovariene la copii și adolescente; (4) evaluarea și perfecționarea aspectelor tehnice ale operațiilor organomenajante laparoscopice și clasice în cazul formațiunilor chistice și tumorale ovariene la pacientele pediatrice, inclusiv și în torsiunile anexelor uterine; (5) studierea structurii morfologice și profilului imunohistochimic a formațiunilor chistice și tumorale ovariene la copii și adolescente.

Noutatea şi originalitatea a rezultatelor obţinute: A fost doveditcă în cazul TAU este justificată efectuarea detorsiei (etapate) pentru nivelarea sindromului de I/R cu efectuarea operațiilor ovaromenajante chist-(tumor-)ectomiilor cu păstrarea maximală a țesutului ovarian la pacientele pediatrice. A fost studiat profilul imunohistochimic (CK-7, CK-20, CEA) în TMCO. În premieră s-a demonstrat că la examenul histopatologic a TOM la pacientele pediatrice mai frecvent se determinau țesuturile stratului mezodermal, de cât a stratului ectodermal și endodermal.

Problema ştiinţifică soluționată: constă înformareaabordurilor metodologice raționale în diagnosticul, stratificarea și tratamentul chirurgical optimal al chisturilor și tumorilor ovariene la copii și adolescente îndreptată spre efctuarea maximală a intervențiilor ovaromenajante și păstrarea funcției reproductive.

Semnificaţia teoretică: Este fundamentată importanța metodelor radiologice în stratificarea preoperatorie a TE la copii și adolescente. Este prezentată compoziția elementară a structurilor osteo-dentare ale TOM în baza microscopiei electronice de scanare (raster), urmată de microanaliza spectrală cu raze X a substanței solide folosind metoda spectroscopiei energodispersivă cu raze X.

Valoarea aplicativă a lucrării: Sunt argumentate și formulate principiile de bază ale diagnosticului și tratamentului chirurgical al CO și TO la copii și adolescente. Sunt detaliat elucidate rezultatele utilizării oncomarkerilor (AFP, CA 125, CEA și CA 19.9) în perioada preoperatorie în CO și TO la copii și adolescente, precum și frecvența rezultatelor fals-negative și fals-pozitive. Detaliat sunt descrise aspectele intervențiilor ovaromenajante în cazul CO și TO benigne. Sunt prezentate aspectele tehnice ale intervențiilor chirurgicale în cazul formațiunilor ovariene de volum la pacientele pediatrice inclusiv în TAU, formațiunilor ovariene gigantice (>15 cm), tumorilor ovariene mucinoase, chisturilor paraovariene și parazitare etc. Sunt elucidate etapele operațiilor cu folosirea tehnologiilor laparoscopice, precum și tumor-(chist-)ectomiile extracorporale laparoscopic asistate.

Implementarea rezultatelor ştiinţifice: În bazaacestui studiu au fost implementate noi metode de tratament a chisturilor și tumorilor ovariene la copii și adolescente în secțiile de ginecologie chirurgicală, secția de ginecologie pediatrică, secția chirurgie pediatrică urgentă al IMSP Institutul Mamei și Copilului (Chișinău, Republica Moldova) și în procesul didactic a Departamentului Obstetrică și ginecologie, disciplina obstetrică și ginecologie, catedrei chirurgie, ortopedie și anesteziologie pediatrică a Universității de Medicină și Farmacie „Nicolae Testemițanu”. În baza rezultatelor studiului au fost obținute 2 drepturi de autor și 10 acte de implementare în practica medicală.

Резюме

Харя Патричия «**Диагностика и лечение кистозных и опухолевидных образований яичников у детей и подростков**». Диссертация на соискание ученой степени кандидата медицинских наук, Кишинев, 2021. Диссертация состоит из введения, 4 глав, синтеза полученных результатов, выводов, практических рекомендаций, 21 таблиц, 133 рисунков. Библиография включает 295 источников. По теме диссертации опубликовано 27 печатных работ.

Ключевые слова: дети, подростки, кисты яичников, доброкачественные, злокачественные, опухоли яичников, перекрут яичника, ишемия/реперфузия, онкомаркеры, ультразвук, допплер, компьютерная томография, магнитно-ядерная томография, хирургическое лечение, лапароскопическая кистэктомия, органосохраняющие операции.

Область исследования: 321.15 – акушерство и гинекология

Цель работы: Улучшение результатов хирургического лечения кистозных образований и опухолей яичников у детей и подростков на основании оптимизации лечебно-диагностичского менеджмента, а также оценки ближайших и отдаленных результатов лечения.

Задачи исследования: (1) изучить клинические манифестации кистозных образований и опухолей яичников у детей и подростков; (2) установить радиологические особенности кистозных образований и опухолей яичников у педиатрических пациентов; (3) определить информативность онкомаркеров при кистах и опухолях яичников у детей и пдростков; (4) разработать и улучшить технические аспекты лапароскопических и традиционных органо-сохраняющих вмешательств при кистозных образованиях и опухолях яичников у педиатрических пациентов, включая и перекруты придатков матки; (5) определить морфологическую структуру и иммуногистохимический профиль кистозных образований и опухолей яичников у детей и подростков.

Новизна и оригинальность исследований: Доказано, что при ППМ целесообразно выполнение дозированной (поэтапной) деторсии для нивелирования I/R синдрома и выполнения органосохраняющих вмешательств кист-(тумор-)эктомии с максимальным сохранением ткани яичника у педиатрических пациенток. Изучен иммуногистохимический профиль (CK–7, CK–20, CEA) при МОЯ. Впервые продемонстрировано, что при гистопатологическом исследовании ЗТЯ у педиатрических пациенток чаще отмечены ткани мезодермального слоя, чем ткани эктодермальниго и эндометрального слоев.

Решенная научная проблема: состоитв создании методологии рациональных подходов в диагностике, стратификации и оптимальном хирургическом лечении кист и опухолей яичника у детей и подростков направленной на максимальное выполнение органосохраняющих вмешательств и сохранения репродуктивной функции.

Теоретическая значимость: Обоснована важность радиологических методов в предоперационной стратификации ОЯ у педиатрических пациенток. Представлен элементный состав костно-дентальных структур ЗТЯ на основании сканирующей (растровой) электронной микроскопии с последующим рентгено-спектральным микроанализом твёрдого вещества с использованием метода энергодисперсионной рентгеновской спектроскопии.

Практическая значимость: Аргументированы и сформулированы основные принципы диагностики и хирургического лечения КЯ и ОЯ у детей и подростков. Подробно освященырезультаты использованияонкомаркеров(AFP, CA 125, CEA и CA 19.9) в предоперационном периоде при КЯ и ОЯ у детей и подростов, а так же представлена частота фальс-негативных и фальс-позитивных результатов. Детально описаны технические аспекты оваро-сохраняющих вмешательств при доброкачественных ОЯ и КЯ. Представлены технические аспекты оперативных вмешательств при объемных образованиях яичника у педиатрических пациенток в т.ч. при ППМ, гигантских (>15 cm) образованиях яичника, муцинозных опухолях яичника, параовариальных и паразитарных кистах и т.д. Освящены этапы операций с использованием лапароскопических технологий, а так же лапароскопически-ассистированых экстракорпоральных тумор-(кист-)эктомий.

Внедрение научных результатов: На основании данного исследования внедрены новые методы диагностики и лечения кист и опухолевидных образований яичников у детей и подростков в отделениях оперативной гинекологии, детской гинекологии, детской срочной хирургии Института матери и ребенка (г.Кишинев, Республика Молдова), а также в педагогическом процессе Департамента Акушерства и гинекологии и кафедры детской хирургии, ортопедии и анестезиологии Университета медицины и фармации им. Н.Тестемицану. По результатам исследования получены 2 авторских права и 10 актов по внедрению в медицинскую практику.

Summary

Patricia Harea **"Diagnosis and surgical treatment of cysts and ovarian tumors in children and adolescents".** Thesis for obtaining degree of candidate of medical sciences, Chisinau, 2022. The thesis includes introduction, 4 chapters, synthesis of results, general conclusions, practical recommendations, 21 tables, 133 figures. The bibliographic index with 295 sources. On the topic of the thesis, 27 scientific papers were published.

Keywords: children, adolescents, ovarian cysts, benign, malignant tumors, ovarian tumors, ovarian torsion, ischemia / reperfusion, tumor markers, ultrasonography, Doppler, computer tomography, magnetic resonance imaging, surgical treatment, laparoscopic ovarian cystectomy, organ-preserving surgery.

Field of study: 321-15 - obstetrics and gynecology

Aim of the study: Improving the results of surgical treatment in ovarian cysts and tumor formations in children and adolescents, based on optimizing diagnostic-curative management and estimating early and late results of the treatment.

The objectives of the study: (1) to study the particularities of clinical manifestations of cysts and ovarian tumor formations in children and adolescents; (2) determination of the imaging features of the cysts and ovarian tumor formations in pediatric patients; (3) assessment of the informativeness of tumor markers in the diagnosis of ovarian tumor formations in children and adolescents; (4) evaluation and improvement of the technical aspects of laparoscopic and classical organ-spearing operations in the case of cystic and ovarian tumor formations in pediatric patients, including in torsions of the uterine adnexas; (5) to study the morphological structure and immunohistochemical profile of ovarian cysts and tumor formations in children and adolescents.

Novelty and originality of the results obtained: It has been proven that it is expedient to perform dosed (staged) detorsion in AT to avoid the I/R syndrome and perform organ-preserving interventions of cyst-(tumor-)ectomy with maximum preservation of ovarian tissue in pediatric patients. The immunohistochemical profile (CK-7, CK-20, CEA) in MOC was studied. It has been demonstrated for the first time that in histopathological examination of MOT in pediatric patients, tissues of the mesodermal layer are more often noted than tissues of the ectodermal and endodermal layers.

Scientific problem solved: is to create a methodology for rational approaches to the diagnosis, stratification and optimal surgical treatment of ovarian cysts and tumors in children and adolescents aimed at the maximum implementation of organ-preserving interventions and the preservation of reproductive function.

Theoretical significance: The importance of radiological methods in the preoperative stratification of OC in pediatric patients is substantiated. The elemental composition of the bone-dental structures of the MOT is presented on the basis of scanning (raster) electron microscopy followed by X-ray spectral microanalysis of a solid substance using the energy-dispersive X-ray spectroscopy method.

Applicative value of the paper: The basic principles of diagnostics and surgical treatment of OC and OT in children and adolescents are argued and formulated. The results of the use of oncomarkers (AFP, CA 125, CEA and CA 19.9) in the preoperative period for OC and OT in children and adolescents are discussed in detail, as well as the frequency of false-negative and false-positive results. The technical aspects of ovaro-sparing interventions for benign OT and OC are described in detail. The technical aspects of surgical interventions for ovarian masses in pediatric patients, incl. with AT, giant (>15 cm) ovarian masses, ovarian mucinous tumors, paraovarian and parasitic cysts, etc. The stages of operations using laparoscopic technologies, as well as laparoscopically-assisted extracorporeal tumor-(cyst-)ectomy are consecrated.

Implementation of scientific results: Based on this study, new methods of treatment of pediatric patients with ovarian cysts and tumors were implemented in the surgical gynecology departments, Pediatric gynecology department, Urgent pediatric surgery department of IMSP Mother and Child Institute (Chisinau, Republic of Moldova) and in the teaching process of the Department of Obstetrics and Gynecology, Obstetrics and Gynecology, Department of Pediatric Surgery, Orthopedics and Anesthesiology of the University of Medicine and Pharmacy "Nicolae Testemitsanu". Based on the results of the study, 2 copyrights and 10 acts of implementation into medical practice were obtained.