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Diagnostic and treatment strategies in pediatric ovarian cystic lesions

PhD. THESIS ABSTRACT

Scientific coordinator:
PROF. UNIV. DR. VASILE SÂRBU

Doctoral student:
FLOREA (ŞTEFANOPOL) IOANA ANCA

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INTRODUCTION

The field of pediatric gynecology has developed at an extremely rapid pace in recent years, as an adaptive response to the rising frequency in female reproductive tract diseases, under the age of 18. In 1940, Professor Rudolf Peter founded the first department of Pediatric Gynecology in Prague and, in 1971, in Lausanne, the International Federation of Child and Adolescent Gynecology was established. In many other countries there are similar national societies: Italy (1978), the United States (1986), Great Britain (2000), with the aim of training pediatric surgeons with experience in this pathology. Although there is still no consensus on the management of pediatric cystic ovarian lesions, treatment schemes have been proposed that take into account the patient's age, symptoms, menarcheal status, the size and the ultrasound image of the lesion.

The diagnosis of "ovarian cyst" generates anxiety among patients of any age, the smaller the age at which it is detected the greater the psychosocial impact it has on their families. The increasing prevalence of ovarian cystic lesions (OCL) in pediatric patients, the large number of medical specialties involved in their management, but also the lack of a national consensus on their diagnosis and, especially, on their treatment, were the reason why I chose this research topic for the present doctoral thesis.

In an age where terms such as screening, prediction or prevention are used in all medical fields, paraclinical methods of diagnosis are of paramount importance. The accessibility and relatively low cost of an abdominopelvic ultrasound exam have made it become the first-line imaging method in the investigation of female internal genitalia.

On the one hand, technological advances in recent years, as well as the increasing ability of imaging specialists in ultrasonographic exploration of the female pelvis, have made it possible to adopt a more conservative attitude in the treatment of ovarian cystic lesions. However, on the other hand, the visualization of infracentimeter ovarian cystic masses could cause an overestimated diagnosis, creating a false increased incidence.

Not long ago, it was considered that, in childhood, the ovary was in a state of functional hibernation, hormonally inactive and without structural changes, which is why ovarian cystic lesions were considered a rare pathology in small ages, not included in the differential diagnosis of abdominal pain. Moreover, once an adnexal mass was discovered at an early age, its exploration by means of laparotomy, most often followed by oophorectomy was considered mandatory. Because postoperative histopathological examination showed that

most lesions were functional or benign, and because the increased concern for preserving future adult fertility was an irrefutable reality, pediatric surgeons were faced with the need to change their therapeutic attitude from an aggressive oophorectomy, which was handy but often unjustified, to more risky and laborious ovarian preservation techniques.

A major problem of modern society is being overweight. Considered to have a pandemic spread at the level of the entire population, with obvious negative implications on any apparatus or system, obesity has been the study object of much modern research. Although the etiopathogenic mechanism is yet incompletely elucidated, more and more scientific papers suggest the existence of a correlation between excess adipose tissue and the hypothalamic-pituitary-ovarian axis, with worrying consequences on fertility, proper functioning of the ovarian cycle, and the appearance of ovarian cyst lesions.

The correct interpretation of the clinical and imaging information, together with the adequate pathological classification of the ovarian lesion, require thorough knowledge of embryogenesis, of the physio-histology and of the normal ultrasound characteristics of the female adnexa. For this purpose, the first chapter of the thesis will consist in laying out the physiological and pathological aspects based on an in-depth study of the specialized literature, and in illustrating them with images from my personal casuistry. The second chapter focuses on the study of ovarian cystic lesions, both at the level of the whole group of patients and, separately, at the level of two subgroups of premenarcheal and postmenarcheal girls, in order to highlight, by comparing the results, the existence of differences in OCL diagnosis, evolution, treatment and prognosis.

All the studies of this doctoral thesis will converge towards the development of a diagnosis and treatment protocol for pediatric OCLs, applicable both at the level of the first medical units that evaluates patients, that is the GP's practices, and at the level of the other medical specialties involved. I will scientifically argue why not all OLCs should be labelled as "ovarian cysts" when, in fact, it could be just a physiologically evolving ovarian follicle, and I will also emphasize the need for conservative treatment as the first option whenever possible.

I. CURRENT STATE OF KNOWLEDGE

The information contained in this chapter, obtained by means of an in-depth study of the specialized literature, can be found in the doctoral thesis and it is not included in the present abstract, which contains only personal research.

II. PERSONAL CONTRIBUTION

II.1. Working hypothesis

OCL at a pediatric age forms a medical entity characterized by a non-specific clinical picture and by an extremely varied ultrasound and anatomopathological spectrum. Epidemiological studies, which very rarely include groups of more than 150 cases, are equally dispersed, or are extended to all pediatric ages; most studies address a limited segment of OCL pathology, treating only clinical, anatomopathological, or therapeutic aspects etc. Thus, the data from the specialised literature about OCL in children are vast but relatively inconsistent, due to different anatomopathological classifications, to the usual diagnostic methods that do not always allow a definite or clear diagnosis, to the different age of the examined population (from newborns to adolescents) or to studies performed by doctors specialised in different domains (endocrinologists, radiologists, pathologists, gynecologists or pediatric surgeons). Moreover, the management of these patients is heterogeneous, depending on the country, hospital or doctor, not being a unanimously accepted consensus. The only aspect on which there is general agreement is the preservation of as much ovarian tissue as possible, necessary for the normal pubertal development and the preservation of fertility.

There are two major pitfalls in the diagnosis of and the therapeutic approach to OCL: underestimation or overestimation. Performing surgery on any OCL is not justified, given the low risk of malignancy and its self-limiting natural evolution but, on the other hand, the conservative treatment performed at any cost, can increase the potential for complication of OCLs by ovarian torsion or ovarian cyst rupture.

A retrospective study, conducted in Turkey, in 2017, concluded that it is useful to divide OCL patients into age and size groups; there was no standardized management protocol in the participating centres, and the lesions were treated according to the judgment and preferences of the surgeon [93]. Another study, conducted in 2017, in Poland, showed

that, for a correct therapeutic decision, the first step is to recognize the nature of the OCL and the second is the existence of a complete algorithm for diagnosis and treatment, consistent with the patient's age and adapted to the socio- economic development of the country [337].

By means of the present study, we aimed at researching some aspects and at answering some questions:

1. Is OCL incidence in pediatric patients known?
2. Is the OCL correctly diagnosed so that a potential overestimation doesn't result in prescribing an excessive treatment and in inducing a state of panic among patients and their families?
3. Are there risk or prognostic factors for OCL occurrence, treatment and evolution?
4. Are there any late diagnoses, and to what extent a preventive attitude may influence the evolution of an OCL?
5. Which is the optimal surgical choice? If an OCL is discovered intraoperatively, do we operate on it, even if it is only a functional cyst, or do we risk a second procedure if it does not disappear spontaneously?
6. In an era when the minimal invasive approachsems to be the first surgical option in the majority of surgical specialties, is laparoscopy a technique of choice in OCL treatment, accessible to all pediatric surgeons?
7. Is there a diagnosis and treatment scheme in children so that the management of this pathology could be unitary? Is this diagnosis under the influence of the patient’s menarcheal status?

Based on these questions, we decided to research the OCL in pediatric patients, in terms of a multidisciplinary approach, aiming at finding some specific features for the studied age groups and for the ultrasound and anatomopathological types, in order to enable the achievement of the set objectives for this thesis.

II.2. General research methodology

The present doctoral thesisis an analytical, prospective study, the databases including information extracted from the patients’ medical charts, the patients’ clinical records and the patients’ imagistic investigations, found in the archives of The Clinical Emergency Hospital for Children “Sfântul Ioan” Galați, over a 3-year period, between 2017 and 2019. The information on which the summary tables were created comprises the characteristics of 488 patients, aged 0-18, having an OCL ≥ 10 mm, and coming from several sources: general

practitioners, the pediatric ambulatory care units, endocrinology or surgery departments, the clinical and paraclinical hospital departments, and the emergency care unit. OCLs were discovered either on an ultrasound investigationor during surgery.

Ethical considerations

Data collection and processing were performed by complying with the privacy agreement regarding the anonymity of patients.

We also obtained the approval of the Bioethics Commission of the Clinical Emergency Hospital for Children "Sfântul Ioan",Galaţi, in order to access and collect personal information about the patients from the hospital database, archived electronically or on paper (medical charts, operating protocol registries, clinical consultation records), as well as intraoperative images.

II.3. Research objectives

As main objective, this thesis attempts at achieving a modern diagnostic and treatment algorithm for OCL in pediatric patients, depending on their age, symptoms, and echographic features. Its completion was possible by establishing and fulfilling certain secondary objectives, such as:

- OCL epidemiological evaluationat the level of the entire studied sample group;
- clinical, paraclinical and imagistic characterisation of the entire sample group;
- the research on ultrasound efficiency in the OCL diagnosis, and on its value as a screening method for the etiological diagnosis of acute and chronical abdominal pain syndrome;
- establishing the echographic border between physiological and pathological, and some accurate terms to define OCL;
- establishing a therapeutic approach to OCL that is incidentally discovered during surgery;
- evaluating the influence of the main surgical techniques used in the study on the ovarian reserve;
- evaluating the complication occurrence risk, correlated with the patients' age, the OCL echographic and anatomopathological features, and with the type of treatment;
- evaluating the recurrence risk, correlated with the patients' age, the OCL size and anatomopathological type, and with the surgical technique used;

- finding out the menarche average age in a group of patients with a normal ovarian ultrasound;
- the research on a correlation between being overweight, menarche, OCL incidence and menstrual disorders;
- the research on the existence of certain risk and prognostic factors for OCL;
- characterisation, evaluation and statistical comparison of premenarcheal and postmenarcheal patient subgroups.

II.4. Materials and methods

The study group includes a total number of 488 patients from the data base of the Clinical Emergency Hospital for Children "Sfântul Ioan" Galați, selected by relying on the inclusion and exclusion criteria detailed in each chapter from the special part.

In order to select the 488 patients included in the study group, the data collection was initially performed by analysing the electronic data from the imagistic and radiology department and the medical charts from the pediatric surgery department. In the initial stage, there were evaluated 4115 abdominopelvic ultrasounds, visualising the ovaries. In the second stage,we excluded the ultrasounds representing check-ups, thus remaining 3284 patients. In the third stage, we excluded 2827 cases, representing ultrasounds of normal ovaries and patients with one of the exclusion criteria. Finally, we added a subgroup of 31 patients with intraoperatively-discovered OCLs, hence forming the final study group of 488 patients, aged 0-18 years, having an OCL ≥ 10 mm.

In order to identify the incidence of OCL in the general female pediatric population, we compared the 488 patients from the study group to the 3284 patients on which ultrasound examinations were performed (table 2.1).

Table 2.1. Structure of the total sample of patients included in our study

Current number	Institution	Group characteristics	Sample	
			Total number of patients	%
1.	Clinical Emergency Hospital for Children "Sfântul Ioan" Galați	Final main group	488	14.85% of the 3284-patient group
2.		0-12 months of age patient group	10	0.3% of the 3284-patient group
				2.04 % of the main group
3.		Premenarcheal patient group	52	1.58 % of the 3284-patient group
				10.65 % of the main group
4.		Postmenarcheal patient group	426	12.97% of the 3284-patient group
				87.29 % of the main group
Total patients with ultrasound exam			3284	100%

Besides the main group, there were created two other subgroups, whose characteristic swere followed in a comparative manner: one premenarcheal subgroup (52 patients), and one postmenarcheal subgroup (426 patients), depending on the presence and absence of the menarche. At the same time, a third subgroup was studied, consisting of 10 patients aged 0-12 months, whose characteristics were followed within the group of 488 patients.

In order to achieve the proposed objectives, the thesis was structured in 3 studies:

- The first study investigatesthe OCL socio-demographic characteristics and diagnostic methods,by reference to the entire group;
- The second study focuses on the analysis of the OCL treatment, complications and recurrences, at the level of the entire group;
- The third study compares the 2 subgroups (premenarcheal and postmenarcheal), simultaneously analysing the hypothesis of a correlation between the presence of menarche, being overweight, menstrual disorders incidence, and OCLs.

II.5. Statistical methods used to analyse data

All the information served as variables in the final summary table. Sampling lists were drawn up and, subsequently, the main group was subdivided into age groups, OLC characteristics, symptomatology, paraclinical data and therapeutic approach. All the obtained data were entered in an Excel 2019 table and subsequently analysed by using the SPSS v24 software, the causal relationships and existing correlations being investigated. For the graphical representations we used pie charts, bar graphs, scatter plot matrices, linear regression graphs and histograms. We used the T test, the Chi square test, the Pearson, Spearman and Kendall`s Tau correlation coefficients; for the differences between groups, we used ANOVA one way and Levene, as part of the ANOVA test, the Tukey and Bonferroni tests for multiple comparison methods.

Study 1: Socio-demographic analysis and diagnosis methods for OCLs, at the level of the entire sample group

In this chapter we shall study the OCL incidence, as well as its demographic, clinical, paraclinical and imagistic characteristics, in the 488-patient group. The following aspects were looked into:

a) Main objective - determining the incidenceof the main OCL characteristics in the study group, and examining the correlations between them, in order to find possible prognostic factors and to establish a diagnostic algorithm.

b) Secondary objectives:

- determining the OCL incidence in the feminine pediatric population, as well in the study group;
- determining the average age of menarche occurrence in the study group, as compared to a group of patients with normal ovarian ultrasound;
- investigating the demographic characteristics of the patients from the study group, and determining their importance for OCL identification and evolution;
- investigating clinical, paraclinical and imagistic OCL characteristics in the study group, and evaluating their prognostic value;
- studying the ultrasound value for the OCL diagnosis;
- investigating the existence of a discrepancy between the admission and discharge diagnoses;
- establishing certain accurate terms to define OCLs according to their size and echographic aspect;
- evaluating the rural area of origin as a risk factor in OCL occurrence.

OCLs were classified according to size and echographic aspect. Regarding OCL size, we took into consideration the greatest diameter among the 3 sizes (length, width, thickness). OCLs were then divided into small (10-29 mm), medium (30-49 mm), and large(≥ 50 mm). Anechoic, unilocular thin-walled, homogeneous content OCLs were defined as having simple aspect. Complex OCL were defined as being multilocular, thick-walled, with a solid component, with/or without septa, with/or without internal echoes.

II.6.4.1. OCL incidence and demographic analysis

OCL incidence in the general population

The average age of menarche occurrence was of 11.8 years old, with extremes of 7 and 15 years old. We selected a group of 484 admitted patients, whose ovarian ultrasound exams were normal; in their case the average age of menarche was of 12.2 years old, with extremes of 9 and 16 years old. We used the limit of 12 years of age in order to evaluate the general incidence of OCL ≥ 10 mm in premenarcheal and postmenarcheal girls (by reference to the total number of 3284 patients).

Our study was conducted over a period of 3 years, during which time 3284 patients aged between 0 and 18, were examined by ultrasound. The general frequency of OCL ≥ 10 mm was of 14.85%. The incidence of OCL ≥ 10 mm was of 0.3% for the group aged 0-12 months, 1.58% for the premenarcheal group, and 12.97% for the postmenarcheal one. There was an incidence peak of 13.9% at the age of 11 for patients aged 1-11, and a frequency peak of 25.81% at the age of 15, for the 12-18-yearold girls.

OCL distributionin the 488-patient group, according to age

The average age at presentation was of 14.11, the incidence peak being at 15 years of age (value 19.26%) (fig. 2.1), and the largest percentage is represented by the postmenarcheal patients (87.3%) (fig. 2.2).

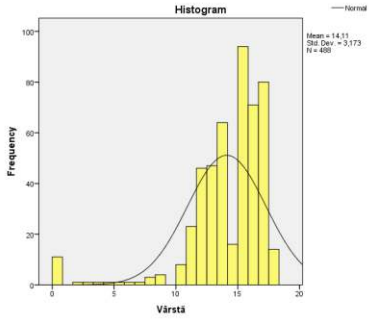


Fig. 2.1. Age distribution histogram

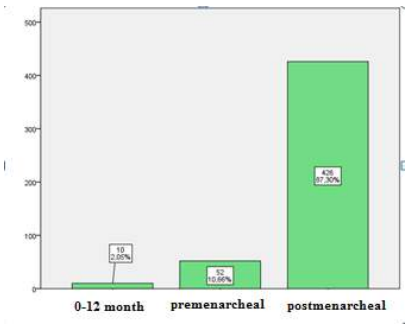


Fig. 2.2. Patient distribution according to age categories

II.6.4.2.1. OCL distribution according to size categories

53.3% were 10-29 mm OCLs (n=260), 34.4% had sizes of 30-49 mm (n=168 cases), and 12.3% were OCLs ≥ 50 mm (n=60). The average size was of 31.90 mm ± 15.782 mm (fig.2.6). We found that, regardless of age, small OCLs were prevalent (fig. 2.7).

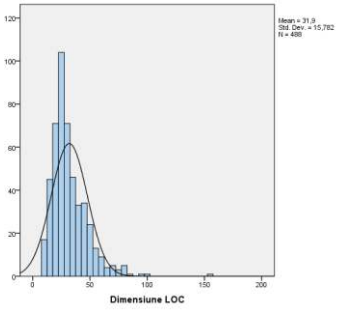


Fig. 2.6. OCL size distribution histogram

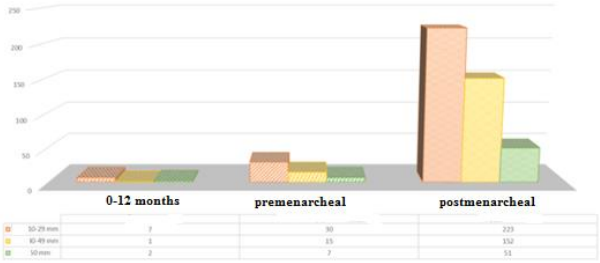


Fig 2.7. OCL size correlated with age groups

Correlation between the size categories and the area of origin of the patient

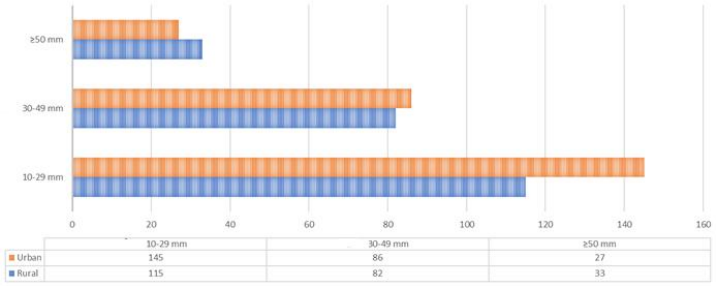


Fig. 2.9. Correlation between OCL size categories and the area of origin of the patient

Although 258 patients were from the urban environment (52.87%), and 230 from the rural environment (47.13%), 55% of the patients from the rural environment had an OCL ≥ 50 mm (fig.2.9).

II.6.4.2.2. OCL distribution according to laterality

Most lesionsare on the right ovary, n = 366 (75%), 92 (18.9%) are unilateral OCLs, on the left ovary and 30 patients (6.1%) had bilateral lesions.

II.6.4.2.3. OCL distribution according to the echographic aspect (simple, complex)

Of the total number of OCLs included in the study, only 93 (19.05%) had a complex aspect, while the remaining 395 (80.94%) were simple.

Correlation between the complex echographic aspect and the area of origin

The sig. statistic index values corresponding to the two bivariate underlying correlations allow us to conclude that, for our study group, large and complex OCLs are more frequent in patients coming from the rural environment (table 2.5).

Table 2.5. T-independent test: cross-correlation (with 2 variables) between the echographic aspect, the area of originand size categories

		N	Corelație	Sig.
Pair 1	Area of origin and the echographic aspect	488	-0.117	0.010
Pair 2	OCL size and the echographic aspect	488	0.501	0.000

Correlation between the OCL aspect, age categories and sizes

Regardless of age,simple OCLs are predominant (fig. 2.2), but 51.61% (n = 48) out of the 93 complex OCLs are of medium size, and 61.66% (n = 37) of the OCLs ≥ 50 mm are complex (p = 0.001).

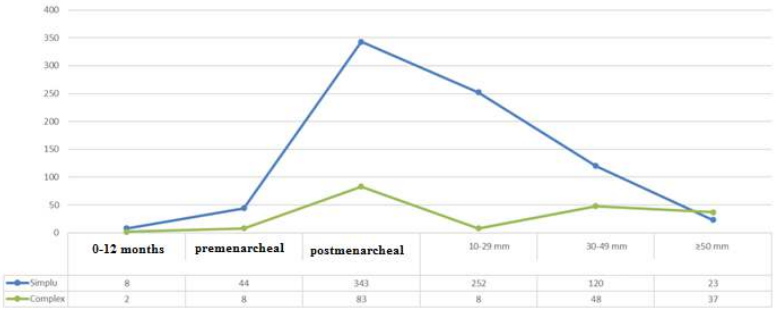


Fig. 2.24. Correlation between the OCL aspect, patients' age, and size categories

Both T independent tests, which were conducted simultaneously, show statistical significance for the correlation between size categories and the echographic aspect, large OCLs being mostly complex, while small OCLs being mostly simple.

Table 2.4. T-independent tests (analysis of the correlation between the OCL aspect, age groups and OCL size categories)

		Test Levene for equality of variances		T- testfor equality of means						
		F	Sig.	t	df	Sig. (2-capete)	Mean difference	Standard error difference	Confidence index 95% Inferior limit	Confidence index 95% Superior limit
Age groups	Variance equivalence assumption	0.839	0.360	-0.485	486	0.628	-0.02287	0.04715	-0.11551	0.06978
	Variance equivalence hypothesis rejection			-0.497	142,619	0.620	-0.02287	0.04603	-0.11386	0.06812
OCL size categories	Variance equivalence assumption	0.128	0.720	-12.775	486	0.000	-0.89157	0.06979	-1.02870	-0.75445
	Variance equivalence hypothesis rejection			-12.464	134,877	0.000	-0.89157	0.07153	-1.03304	-0.75011

II.6.4.3. Planned/unplanned admission, admission diagnosis, ways of OCL detection

The 488 patients participating in this study requested medical advice either in the ambulatory care units, based on a medical referral from the general practitioner (n = 160; 32.7%), or in the emergency care unit (n = 328; 67.3%). After the check-up, it was decided to admit 58 (36.25%) patients who came with a medical referral and 286 (87.19%) patients from the emergency care unit.

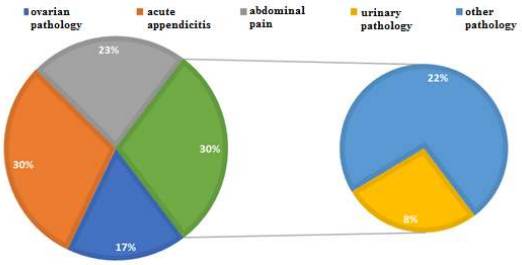


Fig. 2.27. Admission diagnosis incidence

The 344 admitted patients (70.49% out of the total of 488), were referred to the surgical department 190 (55.3%), or to one of the pediatric departments. The largest percentage was represented by those with a diagnosis of acute appendicitis (n = 104; 30.2%), only 17.4% (n = 60) receiving a diagnosis of ovarian pathology (figure 2.27). I would like to emphasize the fact that an ultrasound was not always requested before patient admission.

Diagnosis efficiency by means of an ultrasound examination. Correlation between the area of origin - ways to detect OCL

There were two ways to detect OCL: intraoperatively (n = 31; 6.4%), or during an abdominopelvic ultrasound examination (n = 457; 93.6%). Consequently, we can conclude that the ultrasound had a 93.6% positive predictive value, which was statistically significant according to the chi square test.

Table 2.7. Pearson Chi-square test: correlation between the area of origin and the way of OCL detection

		Way of OCL detection
Area of origin	Chi-square	4.015
	df	1
	Sig.	.045*

Among the 457 patients whose OCL was detected during an ultrasound examination, there are 8% more cases from the urban environment, but among the 31 patients whose OCL was discovered during surgery, there were 30% more from the rural environment, the relationship between these two variables being statistically significant for a $p < 0.05$ (table 2.7).

II.6.4.4. Analysis of main signs and symptoms

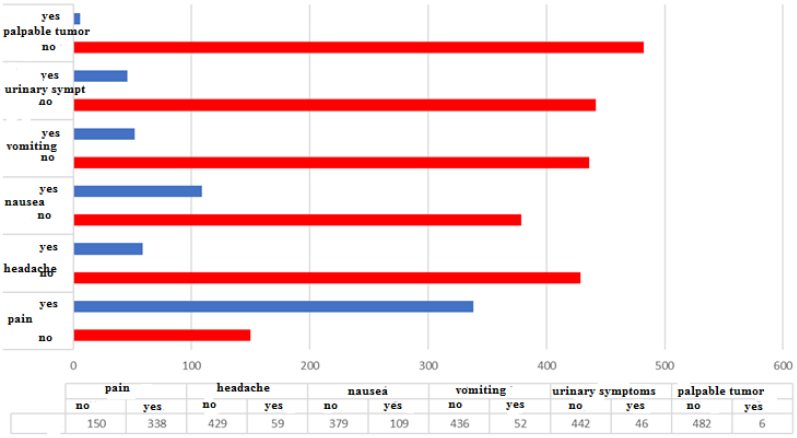


Fig. 2.31. Symptom incidence in the entire study group

The most frequent symptoms which requested a medical check-up were: abdominal pain, headache, nausea, vomiting, and dysuria or pollakiuria (fig. 2.31). Among the objective signs, specific for ovarian pathology, we decided to follow only the palpation of a tumour mass.

Table 2.9. Pearson bivariate correlations between the main symptoms and other OCL characteristics

		Age groups	OCL aspect	OCL size groups	Pain	Vomiting	Palpable tumour	Operated patients	Operated OCL	OCL complications
Pain	Pearson Correlation	0.151**	0.176**	0.181**	1	0.201**	-0.006	0.303**	0.150**	-0.369
	Sig. (2-tailed)	0.001	0.000	0.000		0.000	0.890	0.000	0.001	0.058
	N	488	488	488	488	488	488	488	488	27
Vomiting	Pearson Correlation	-0.022	0.204**	0.146**	0.201**	1	0.082	0.258**	0.212**	0.108
	Sig. (2-tailed)	0.634	0.000	0.001	0.000		0.070	0.000	0.000	0.590
	N	488	488	488	488	488	488	488	488	27
Palpable tumor	Pearson Correlation	-0.324**	0.135**	0.172**	-0.006	0.082	1	0.214**	0.373**	0.544**
	Sig. (2-tailed)	0.000	0.003	0.000	0.890	0.070		0.000	0.000	0.003
	N	488	488	488	488	488	488	488	488	27
**.The correlation is statistically significant for p < 0.01 (2-tailed).										

By corroborating the information from the bivariate correlation table with the Pearson index (table 2.9), we could draw a series of conclusions relating to the symptom incidence, by reference to certain OCL characteristics.

Each of the two symptoms (as well as the palpable tumors) represents, when treated independently, an alarm factor for the patient evolution, but the simultaneous association of pain with vomiting, and tumor mass palpation, represents a predictive factor for the necessity of a subsequent surgical treatment. For our group of patients, it was statistically proven that the simultaneous presence of the three symptoms, associated with large and complex OCLs, represents a clear indication for a surgical approach.

II.6.4.6. Analysis of discharge diagnoses

Discharge diagnoses recorded the same variety as the admission ones, so they were classified into two groups: ovarian pathology and other pathologies. The ovarian lesions that served as a main or secondary discharge diagnosis, which are shown in table 2.13, were the following: ovarian inflammation, microcystic ovary, micropolycystic ovary, polycystic ovary, ovarian cyst or ovarian torsion (the last two diagnoses were classified as OCLs).

Table 2.13. Summary table fordiagnoses, relative to OCL size groups

		OCL size groups		
		10-29 mm	30-49 mm	≥ 50 mm
Admission diagnoses	Ovarian pathology	8	21	27
	Acute appendicitis	50	44	13
	Abdominal pain	47	26	6
	Urinary pathology	16	9	2
	Other pathologies	44	28	2
Discharge diagnoses	OCL	28	44	42
	Microcystic ovary	9	3	1
	Micropolycystic ovary	8	0	0
	Polycystic ovary	27	10	0
	Ovarian inflammation	12	3	0

As it is shown, there is a significant discrepancy (the Pearson index ofthe Chi square test is 0.001) between the admission and discharge diagnoses, fact which is explained not by the ultrasound inefficiency to establish an accurate diagnosis, but by the lack of this investigation before patient admission. One of the aims of the present thesis is to turn the abdominal ultrasound exam into a routine investigation for all patients with abdomino-digestive symptoms. Regarding the secondary discharge diagnoses used in this study, in the subchapter “Discussions”, we will show which are the echographic features corresponding to each pathology.

II.6.5. Discussions

As shown by statistical analysis, the incidence of OCL ≥ 10 mm in the general pediatric population was of 14.85%, the frequency peak corresponding to the age of 15. This is consistent with the high percentage of postmenarcheal patients (87.3%), but also with the pathophysiological mechanism of most OCLs, namely the existence of an AHHO with a cyclic activity (incompletely developed in premenarcheal girls) but with disorders of the feedback mechanisms, fact which leads to either lack of ovulation or persistence of the corpus luteum [64, 67, 69, 70, 71, 74]. A study, similar to the present research, was conducted by Emeksiz et al. [62], the incidence found being of 13.1%, with an incidence peak also at 15 years of age; this slightly lower value as compared to our study can be explained by the fact that the authors did not include patients younger than 5 years of age.

The average age at presentation was 14.11 ± 3.17 years, the extremes being 0 and 18 years of age. There are few studies covering the entire spectrum of pediatric ages (0-18), and most of them are performed on small groups of hospitalized patients; the present study also includes non-hospitalized patients, who presented and received treatment recommendations either in the specialized outpatient clinic or in the Emergency Care Unit. In addition, the studies are conducted by doctors with different specialties, which means that patients were selected according to the specifics of the department. The age-centred classification from this thesis was not found in any other study, most studies establishing the age subgroups as prepubertal and postpubertal patients [62, 93, 121, 146, 340]; even under these conditions, OCLs were proven to be significantly more common for pubertal patients. In terms of age distribution, the vast majority were postmenarcheal patients (87.30%). Kirkham et al. [209] studied 2 subgroups: premenarcheal (but also included patients younger than 1 year of age) and postmenarcheal, finding incidences of 14.9% and 77.1%, respectively. In the light of the above, we may assert, the same as other authors [52, 64, 180, 331, 209], that OCLs mainly occur in menstruating patients.

The rural area of origin proved to be a risk factor, but also an element of negative prognosis (large, complex OCLs, discovered intraoperatively), since there is lower compliance with both access to primary health care or to technical diagnostic methods (medical test laboratory, ultrasound equipment), as well as the possibility of coming to the necessary check-ups in order to follow the evolution and potential complications.

By corroborating the information obtained in this first study, the conclusion that OCLs in pediatric patients are mostly small, simple, unilateral and on the right side is obvious. The same overwhelming prevalence regarding the three OCL characteristics listed

above was noticed by most of the authors who studied them [61, 62, 93, 272]. The prevalence of OCL on the right ovary could be scientifically explained by the finding that ovulation, which is the basis of the pathophysiological production mechanism for most ovarian cysts, occurs mainly in the right ovary, which has a larger arterial Doppler size and flow, but also an increased DNA and protein content (363, 364, 365, 366, 367, 368). A more practical explanation would be that acute appendicitis is a much better-known pathology by the population, so that the pain in the right iliac fossa, rather than in the left iliac fossa, determines a visit to the doctor. Another statistically significant finding was that the vast majority of large OCLs (61.66%) have a complex aspect.

The most common symptom in the group of 488 patients was pain, present in 69.26% of cases. The same as our study, most studies in the literature [52, 60, 61, 63, 93, 146, 147, 175, 179, 180, 340] highlighted pain as a prevalent symptom, and the palpation of a tumour mass as a clinical sign, always associated with large ovarian lesions that required surgical treatment.

According to the study conducted by Caprio et al. [254], the normal ovary on an ultrasound exam can be of several types: homogeneous, microfollicular (with less than 4 follicles of 3-5 mm), multifollicular (with more than 5 follicles of 5-10-mm, located in the stroma) (fig. 2.37), multifollicular with a dominant follicle (with 1-2 follicles larger than 13 mm) (fig. 2.38), and polycystic (more than 10 follicles of 3-8 mm, located in the cortex or the stroma).

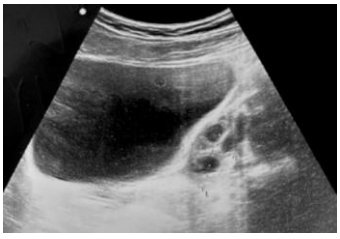


Fig. 2.37. Postmenarcheal patient, 15 years old, ovary with a mutifollicular ultrasound appearance

Fig. 2.38. Postmenarcheal patient, 14 years old, multifollicular ovary with a dominant follicle

In the present study, there were 60 patients who were discharged with the diagnosis of microcystic or micropolycystic or even polycystic ovary, although the ultrasound examination showed only the presence of a single OCL in the right or left ovary, larger than 10 mm. Since these diagnoses induce anxiety in patients and the false idea of an adnexal

pathology, we suggest replacing them with more specific terms, such as follicular structure, ovarian follicle, or functional cyst, as appropriate.

As an overview of all the elements mentioned above, we are thus able to deliver a preliminary presentation, in a staged manner, regarding the management algorithm of a patient diagnosed with OCL, by means of an ultrasound examination:

- Initially, the ultrasound examination will be performed on all patients with abdominal pain or vomiting. If the ultrasound will detect a large OCL (≥ 50mm), and with a complex ultrasound appearance, the hypothesis of surgery will be taken into account (by the clinical judgment of the attending physician).
- On the other hand, if the patient who came at the hospital simultaneously associates pain, vomiting and a palpable tumour, and the result of the ultrasound examination will indicate the presence of a large and complex cystic ovarian lesion, surgery will be the best choice for the treatment of OCL.
- It may be asserted that the potential management algorithm of pediatric patients diagnosed with OCL has relative and absolute indications for surgery (by corroborating the clinical elements with the ultrasound detection of OCL characters).

Study 2: Therapeutic approach, complications and evolution of OCLs, studied atthe level of the entire sample group

II.7.2. Study objectives

Main objective: the therapeutic characterisation of the entire group and finding correlations with the main OCL parameters, in order to establish an accurate treatment algorithm, adequate to pediatric ages.

Secondary objectives

- To establish a therapeutic approach to OCL, which is incidentally discovered during surgery, and the opportunity for circumstantial appendectomy;
- To evaluate the influence of the main surgical techniques, applied in our study, on the ovarian reserve;
- To evaluate the occurrence risk of complications, correlated with the patients' age, the OCL echographic and anatomopathological characteristics, and with the type of treatment;
- To evaluate the recurrence risk, correlated with the patients'age, OCL size and anatomopathological characteristics, and with the type of treatment;

- To evaluate the rural area of origin as a risk factor for the surgical treatment and the evolution of OCL;
- To investigate the efficiency of the ultrasound examination in the diagnosis of complications, and its predictive value for the anatomopathological type of OCL.

II.7.3. Materials and methods

In this subchapter, the study was conducted on the same group of 488 patients, with the same age and size categories, as described above. There will be taken into account both the OCL echographic aspect and the main symptoms (pain, vomiting, palpable tumour). It was considered as conservative any therapeutic approach without a surgical intervention on the ovary; for this reason, patients whose OCL was detected intraoperatively, but without ovarian surgery, was also considered as conservatively managed. The surgical techniques on the ovary, that didn't lead to a salpingo-oophorectomy, were called ovarian sparing surgeries (OSS).

In the beginning, a subgroup of 104 patients, who had a laparotomy, will be studied. Among them, 31 had normal or unvisualized ovaries on ultrasound, OCL being diagnosed intraoperatively; in the remaining cases, who had an ultrasound-diagnosed OCL, the surgical intervention was necessary either because of an acute abdomen clinical picture, or because of symptom persistence after a few days of symptomatic and/or antibiotic medical treatment. This group was studied in order to outline certain indications for surgical or conservative management in OCL, after which they will be confirmed, refuted or reinforced by other statistical tests. In the next stages, we studied a subgroup of 40 patients with surgically-treated OCL, a subgroup of 24patients with complicated OCL, and a subgroup of 31 patients whose OCL was discovered intraoperatively, the role of these studies being to establish a therapeutic approach, adequate to those circumstances. Finally, we laid out the conservative treatment and the evolutionof OCL included in this thesis.

II.7.4. Results

II.7.4.1. Incidence of treatment types for OCL

For the 488 patients included in our study, the treatment was surgical (8%) or conservative (92%) (fig. 2.39).

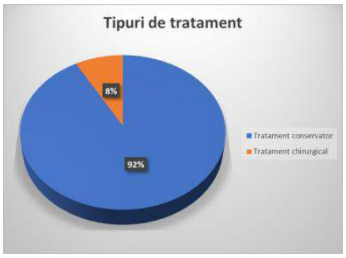


Fig. 2.39. Types of treatment used for the whole group

The figure 2.40 shows that, although only 40 OCLs were operated, there were 104 surgical procedures: 17 cases (17.34%) when the surgical technique addressed only the ovarian lesion (only one lesion was discovered intraoperatively), 23 patients (22.11%) who simultaneously had an appendectomy (14 lesions discovered intraoperatively) and 64 cases (61.53%) when the appendectomy was the only surgical procedure (16 OCLs discovered intraoperatively); in these 64 situations the decision was made to monitor the OCL on ultrasound, without surgery, which classifies this treatment as conservative.

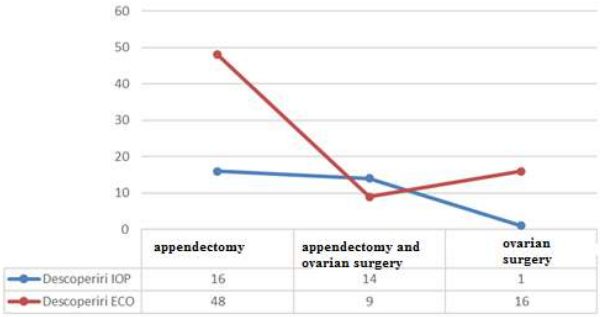


Fig. 2.40. The type of surgical procedure depending on the OCL detection manner

II.7.4.3. Correlation between the surgical procedure types and the OCL size

Table 2.16. ANOVA Test: types of surgical procedures correlated with the OCL sizes

		N	Mean	Standard deviation	Standard error	95% Confidence interval		Minim	Maxim	Variance between elements
						Inferior limit	Superior limit			
Appendectomy		64	29.11	9.962	1.245	26.62	31.60	12	58	
Appendectomy and OCL surgery		23	46.17	21.792	4.544	36.75	55.60	17	100	
OCL surgery		17	71.88	25.908	6.284	58.56	85.20	45	154	
Total		104	39.88	22.724	2.228	35.46	44.29	12	154	
Model	Fixed Effects			16.483	1.616	36.67	43.08			
	Random Effects				14.296	-21.64	101.39			444.101

Table 2.16 presents a statistical descriptive analysis o fthe surgical procedures for the 104 patients, correlated with the OCL sizes.

The OCL average size was of 29.11 mm for the 64 patients with appendectomy, 46.17 mm for those who had an appendectomy and OCL surgery at the same time, and 71.88 mm for those who had only OCL surgery. There were operated mainly OCL with an average size of 46.17 mm ± 21.792 mm, avoiding the excision of an OCL smaller than 29.11 mm. Thus, we can conclude that, for our study group, average-size OCLs were surgically treated starting from 46 mm, avoiding small OCL excision.

II.7.4.4. OCL surgical treatment

Figure 2.44 shows the distribution of the 40 patients whose OCLs were surgically treated, depending on age, lesion size, echographic aspect, and laterality. There were 3 patients (7.5%) operated at the newborn (2) or infant (1) age, 8 premenarcheal girls (20%), and the majority (n = 29; 72.5%) were postmenarcheal girls. By taking into account the number of patients from each category, we will find that the surgical treatment was preferred for 30% ofthe 0-12 months girls, 15.38% of the premenarcheal ones and 6.8% of the adolescents.The average age was 14, with extremes at 4 days old and 17 years old.

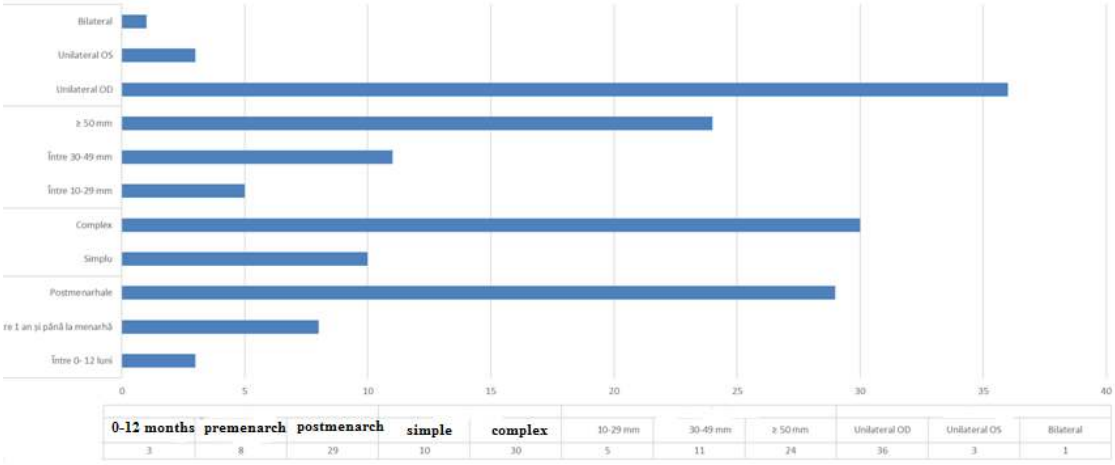


Fig. 2.44. Distribution of the 40 operated OCLs, depending on age groups, aspect, lateralityand size categories

There were 5 small (12.5%), 11 medium (27.5%) and 24 large (60%)OCLs. The average size wasof 57.1 mm, with extremes of 17 mm and 154 mm. If we refer to the total number of cases for each size category,we will find that the decision to perform surgery was made for 1.92% of small OCLs, 6.54% of medium lesions and 40% of large ones. So, the risk for surgery as a treatment method increases together with the OCL sizes.

II.7.4.5. Anatomopathological types of operated OCLs

The main anatomopathological types discovered for the 40 operated OCLs, were: non-neoplastic lesions (n = 28; 70 %) and benign neoplasms (n = 12; 30%). Among the non-neoplastic lesions there were 16 follicular cysts (40%) and 12 corpus luteum cysts (30%), and the benign neoplasms were 9 serous cystadenomas (22.5%) and 3 cystic mature teratomas (7.5%), as shown in figure 2.49.

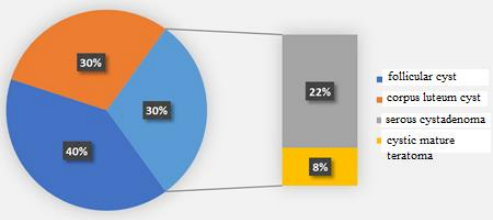


Fig. 2.49. Anatomopathological exam for operated OCLs

By gathering all the information, we can conclude:

- A small, simple OCL is most probably a follicular cyst;
- A medium, complex OCL (associated with pain) is most probably a corpus luteum cyst;
- A large, complex OCL is most probably a benign neoplasm

II.7.4.6. Surgical techniques used in OCL treatment

The surgical techniques used for the 40 OCLs were: 14 cystectomies (CE), 18 stripping techniques, 6 salpingo-oophorectomies (SOE) and 2 ovarian detorsions with CE. In 3 patients, surgery had a laparoscopic approach (2 CE and 1 stripping), but they weren't treated separately, being included in the techniques above. Figure 2.55 shows a detail during a laparoscopic CE for afollicular cystand figure 2.56 shows details during a stripping technique for a corpus luteum cyst.

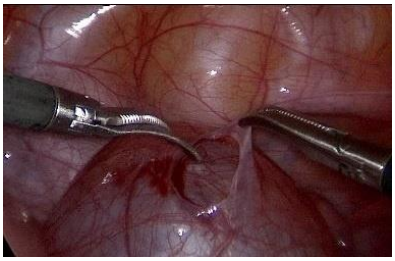


Fig. 2.55. Laparoscopic CE

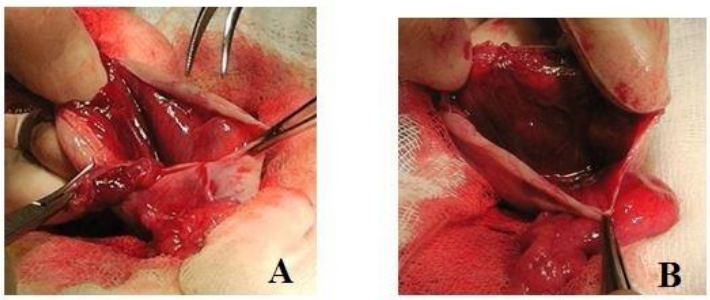


Fig. 2.56. Stripping technique; A: cyst membrane extraction; B: remaining cyst cavity

In order to establish the indication for an accurate surgical technique, depending on the main OCL characteristics (size, aspect), we drew up table 2.30.

Table 2.30. Statistical analysis for the surgical techniques depending on OCL size groups and aspect

				SOE		Cystectomy		Stripping	
				Count	Row Valid N %	Count	Row Valid N %	Count	Row Valid N %
OCL size groups	10-29 mm	Aspect	Simple	0	0.0%	0	0.0%	4	100.0%
			Complex	0	0.0%	0	0.0%	1	100.0%
	30-49 mm	Aspect	Simple	0	0.0%	0	0.0%	2	100.0%
			Complex	1	11.1%	3	33.3%	5	55.6%
	≥ 50 mm	Aspect	Simple	0	0.0%	5	100.0%	0	0.0%
			Complex	5	26.3%	8	42.1%	6	31.6%

By corroborating this information with that from the previous subchapter, we may draw the following conclusions for our study group:

- Small OCLs (regardless of their aspect), but also the medium-simple ones, are usually functional lesions, and can be treated with the help of the stripping technique;
- Medium-complex OCLs, usually are corpus luteum cysts, and they can be treated with the help of the stripping technique and, in case of benign neoplasms, we preferred CE;
- Large OCLs, which are usually benign neoplasms, regardless of their aspect, can be treated with the help of CE.

II.7.4.7. Ovarian reserve and the factors influencing it

By studying the histopathological results for the 40 operated OCLs, more precisely the existence of ovarian tissue on the analysed piece of tissue, with follicles in different stages of maturation, we were able to estimate the extent to which each surgical technique spared the largest amount of ovarian tissue (in the sense that there will be few or no follicles on the examined piece of tissue).

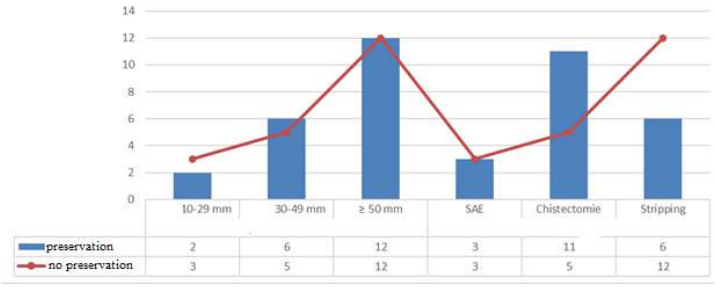


Fig. 2.59. Ovarian preservation depending on OCL size and surgical technique

Figure 2.59 shows the correlation that exists between the ovarian tissue presence on the anatomopathological slides, the sizes and the surgical technique. Thus, we can conclude:

- CE has the biggest ovarian preservation rate (68.75%), the smallest one being for the stripping technique (33.34%) (p = 0,119);
- the larger OCL sizes are the lower the ovarian preservation rate is, reaching a percentage of 60% for large OCLs.

II.7.4.8. Analysis of OCL complications

There are 24 cases of complicated OCLs in our study, 17 (70.84%) being OCLs complicated by rupture and 7 (29.16%) are OCLs complicated by torsion. Figures 2.60 and 2.61 show the macroscopic aspect of 2 OCLs, complicated by rupture, respectively by torsion.

Fig. 2.60. OCL complicated by rupture

Fig. 2.61. OCL complicated by torsion

The incidence of complications was noticed in OCLs with an average size of 38 mm (for the ruptures), or 71mm (for torsions).

According to the Pearson index, with a value which is smaller than the reference value, the aspect and size are predictive factors for complications (table 2.33).

Table 2.33. Pearson bivariate correlations between complications, size and aspect of OCLs

		OCL aspect	OCL size categories	OCL complications
OCL complications	Pearson Correlation	0.210	0.594**	1
	Sig. (2-tailed)	0.324	0.002	
	N	24	24	24

**two-ended statisticallysignificant correlation for values of p<0.01

II.7.4.9. Conservatory treatment of OCLs

448 patients, that is 91.8% of the total number, received conservatory treatment. This consisted in echographic monitoringof the OCL, sometimes associated with symptomatic treatment (mainly non-steroidal anti-inflammatories) or antibiotics (usually used for the pathology that represented the initial admission diagnosis). The OCL's maximum size treated in a conservative manner was of 79 mm, the average size being of 30 mm ±12 mm.

Table 2.38 shows that, for our study group, the therapeutic decision depended on 3 factors: OCL size groups, the echographic aspect, and pain as main symptom. We treated conservatively:

- 97.22% of simple OCLs, and 68.8% of complex OCLs;
- 98% of small OCLs, 93.4% of medium ones and 60% of large OCLs;
- 89% of the patients accusing pain and 75% of those with vomiting;

Table 2.38. Treatment incidence depending on individual variables

						Treatment			
						Conservative		Surgical	
						Mean	Row Valid N %	Mean	Row Valid N %
Mean size						30		57	
Size groups	10-29 mm	Echographic aspect	Simple	Pain	No		*22,1%*		***0,0%***
					Yes		*33,3%*		***10,0%***
			Complex	Pain	No		*0,2%*		***0,0%***
					Yes		*1,3%*		***2,5%***
	30-49 mm	Echographic aspect	Simple	Pain	No		*6,9%*		***0,0%***
					Yes		*19,4%*		***5,0%***
			Complex	Pain	No		*1,8%*		***2,5%***
					Yes		*6,9%*		***20,0%***
	≥50 mm	Echographic aspect	Simple	Pain	No		*1,1%*		***5,0%***
					Yes		*2,9%*		***7,5%***
			Complex	Pain	No		*0,7%*		***0,0%***
					Yes		*3,3%*		***47,5%***

4 risk groups regarding the necessity for surgical treatment were defined:

- patients with small OCLs, regardless of the echographic aspect, but without associated symptoms, do not require surgery;
- patients with medium, simple OCLs and without pain, can be also treated in a conservatory manner;
- a low risk for surgical treatment (2.5%), is reported for small, painful OCLs, (regardless of the echographic aspect);
- the medium risk group (5%) is represented by medium OCLs, that are either simple but painful, or complex (regardless of the pain). Also, in this category, with a similar percentage of surgical procedures (7.5%), are large, simple, painless OCLs;

- the high risk group (47.5%) include OCLs with all the three factors: large size(≥ 50 mm), complex aspect and pain.

Analysis of echographic follow-up

The echographic follow-up was performed regardless of the type of treatment, conservative or surgical. The recommended rhythm was monthly for the first three months from the OCL detection, then at 6 months and 1 year, regardless of the patients' age or OCL size.We noticed that, after a few months, the OCL disappeared spontaneously even if, initially, the lesion increased, or recurred (case in which the new lesion was monitored). We considered recurrence any ipsilateral secondary lesion, belonging to the same anatomopathological type (non-neoplastic or benign neoplasms).

In conclusion, conservatively-treated small OCLs disappeared spontaneously after 1 month in 98% of the cases, and 100% after the second month, with a 2% recurrence rate. 84% medium OCLs disappeared after 1 month, 90% after 2 months, 97.5% after 3 months and, after 6 months, all examined patients had normal ovaries; the recurrence rate was of 5.8%. 70% of large OCLs disappeared after 1 month, 86% after 2 months, 97.5% after 3 months, all patients being cured after 6 months; the recurrence rate was 10%.

The recurrence rate varied depending on the treatment (5% for surgery, 14% for conservative treatment), on the lesion size, on the histopathological type (functional cysts), and on the surgical technique (stripping).

II.7.4.10. Analysis of intraoperatively-detected OCLs

Our study included 31 patients whose ultrasound didn't visualize the ovaries, and the OCL was diagnosed intraoperatively, during the surgery for acute appendicitis. Surgical treatment represented the therapeutic approach to 22.2% (n = 2) of the small OCLs, to 47% of the medium ones (n = 8), and to all 5 large lesions. The average size for operated OCLs was of 48 mm (with extremes of 20 mm and 100 mm), and for those unoperated was of 30 mm (with extremes of 20 mm and of 45 mm). Most small and medium OCLs discovered incidentally weren't operated (77.78% and 53%, respectively), being conservatively treated, without complications; this fact has statistical significance (p = 0.000). Therefore, we can conclude that intraoperatively-detected OCLs, smaller than 50 mm and having simple content, can be treated in a conservative manner, without suspecting any unfavourable evolution.

II.7.5. Discussions

As demonstrated by the first study, the most common OCLs are small (less than 30 mm), simple, and are found in postmenarcheal girls. On the other hand, during a monthly ovarian cycle, one of the ovarian follicles physiologically reaches the tertiary stage (antral, de Graaf), characterized by sizes between 10 - 30 mm [29, 30, 41, 44] and an ultrasound aspect of a simple cyst [251, 254, 256]. After ovulation, the corpus luteum appears, which also has sizes smaller than 30 mm, but a complex ultrasound aspect [277, 281, 282]. For these reasons, but also due to the multiple specialized studies that demonstrate the natural evolution to spontaneous disappearance of the two entities described above (the antral follicle and the corpus luteum), in 2010, the US Society of Radiologists in Ultrasound established that the size of 30 mm represents the minimum diameter of an ovarian cyst, OCLs smaller than 30 mm being considered physiological evolution stages of ovarian follicles [118] and, as such, should not be called ovarian cysts. Moreover, in 2017, the British Society of Pediatric and Adolescent Gynecology drew up a guide for the management of ovarian cysts in girls and adolescents, considering that we can call "ovarian cyst" only OCLs with anechoic content and larger than 50 mm; lesions smaller than 50 mm are considered physiological, provided that the patient has already had menarche [333]. If we also corroborate these data with the results of the conservative treatment, this study shows that it is not necessary to carry out the monthly monitoring of OCLs, especially since their size is less than 30 mm (and, in some cases, even 50 mm), and that, given the low risk of recurrence, after the spontaneous disappearance or lesion surgery, ultrasound reassessment is not necessary at intervals of less than 6 months or even 1 year.

Finally, in order to prove the need for conservative treatment as a first intention for OCLs that have no signs of complication, we will give some examples with the help of some ultrasound images. At the same time, we emphasize the variety of ultrasound forms that the corpus luteum cyst may take, the most common AP type of ovarian cystic lesion with a complex aspect (figures 2.68-2.70).

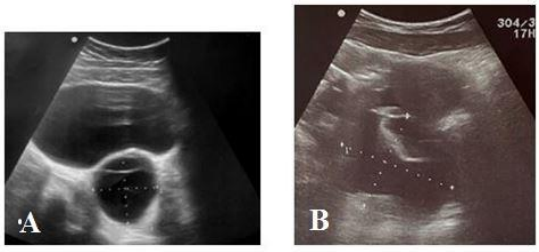


Fig. 2.68. A: 15 years old, postmenarcheal, OCL 56 mm, unoperated; B: 15 years old, postmenarcheal, OCL 58 mm, TCM operated

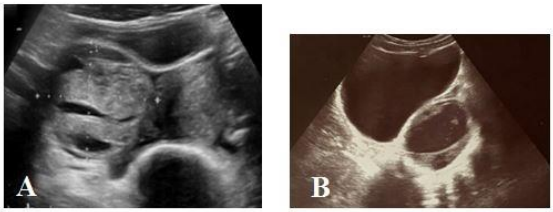


Fig. 2.69. A: 15 years old, postmenarcheal, OCL 72 mm, unoperated; B: 15 years old, postmenarcheal, OCL 66 mm, CAS operated

Study 3: Comparative study of OCL in premenarcheal and postmenarcheal girls

Study objectives

Main objective

The comparative description of both subgroups of premenarcheal and postmenarcheal patients in order to complete the diagnostic and treatment algorithm for pediatric OCLs.

Secondary objectives

- Epidemiologic comparative evaluation of the main clinical and paraclinical OCL characteristics for both studied subgroups;
- To investigate the existence of a correlation between being overweight, the presence of the menarche, OCL incidence and menstrual disorders;
- Comparative analysis of the management for both studied subgroups;
- To establish the ultrasound efficiency by reference to the two subgroups

II.8.3. Materials and methods

We analysed only the premenarcheal and postmenarcheal subgroups, the 10 patients who were younger than 1 year being excluded. We emphasised the differences between them that could influence the therapeutic approachto the evolution of OCLs.

One of the parameters studied in this stage was the body mass index (BMI), patients being classified into 3 groups: underweight, normal weight and overweight; in the last category there were included both overweight and obese patients. We simultaneously studied the incidence of the endocrine symptoms, specific to each subgroup. Thus, for the premenarcheal subgroup we investigated the signs of precocious puberty, and for the postmenarcheal subgroup, we investigated dysmenorrhea and menstrual disorders, especially amenorrhea. *We must emphasize the fact that the endocrinologist was the one to recommend*

and interpret the result of hormonal tests, as well as to establish a specific endocrinological treatment and to monitor how the patient responded to that treatment.

II.8.4. Results

The incidence of OCL ≥ 10 mm, by reference to the 3284 patients with ovarian ultrasound, was of 4.58% for patients aged 1-11 (premenarcheal), and 20.66% for those aged 12-18 (postmenarcheal)

Table 2.47. Summary table for both subgroups, depending on the BMI, OCL aspect and size categories

		Age groups		Sig.
		Premenarcheal	Postmenarcheal	
		Count	Count	
OCL aspect	Simple	44	343	0.477
	Complex	8	83	
BMI groups	Underweight	7	24	0.005
	Normal weight	21	265	
	Overweight	24	137	
OCL size groups	10-29 mm	30	223	0.419
	30-49 mm	15	152	
	≥50 mm	7	51	

Although the percentage of complex lesions was higher for menstruating patients, the percentage of complex OCLs which were surgically treated was significantly higher for the premenarcheal subgroup (75% vs 26.5%).

Among the patients included in this study we found a higher percentage of overweight premenarcheal girls (46.1%) than overweight postmenarcheal girls (32.1%), the difference being statistically significant. As we previously observed, OCLs are more frequent among patients in urban areas than those in rural areas, and the percentage of patients with high BMI is also higher for urban patients, fact which enables us to speculate that being overweight influences the incidence of OCL. The same conclusion may be drawn from the association between the prevalence of overweight premenarcheal girls and large OCLs, as compared to postmenarcheal patients. This conclusion is statistically verified by a chi square equation.

Menstrual disorders were registered for 145 (34%) of the patients included in our study, and we also found a higher percentage of overweight patients (35.7%,as compared to

33% for those with normal weight). The statistical analysis confirms, by means of many chi square $\chi 2$ equations, as well as the statistically significant Pearson coefficients, the fact that obese patients have a higher risk to develop menstrual disorders such as amenorrhea or dysmenorrhea.

From the total number of 40 surgically treated OCLs, 8 (20%) were premenarcheal patients [383] and 29 (72,5%) postmenarcheal. But if we refer to each subgroup separately, we will find an incidence of 15.38% operated premenarcheal patients (from the total of 52) and 6.8% postmenarcheal patients,respectively.

Table 2.51. Summary table for surgical treatment depending on the main OCL characteristics of the 2 subgroups						Premenarcheal			Postmenarcheal		
						Total	PreM	% operate	Total	PostM	% operate
OCL aspect	Simple					44	2	4.55%	343	6	1.75%
	Complex					8	6	75.00%	83	23	27.71%
OCL size groups	10-29 mm					30	0	0.00%	223	5	2.24%
	30-49 mm					15	2	13.33%	152	7	4.61%
	≥ 50 mm					7	6	85.71%	51	17	33.33%
OCL size groups	10-29 mm	OCL aspect	Simple	Pain	No	10	0	0.00%	81	0	0.00%
					Yes	20	0	0.00%	135	4	2.96%
			Complex	Pain	No	0	0	0.00%	0	0	0.00%
					Yes	0	0	0.00%	7	1	14.29%
	30-49 mm	OCL aspect	Simple	Pain	No	4	0	0.00%	27	0	0.00%
					Yes	8	0	0.00%	82	2	2.44%
			Complex	Pain	No	0	0	0.00%	7	0	0.00%
					Yes	3	2	66.67%	36	6	16.67%
	≥ 50 mm	OCL aspect	Simple	Pain	No	0	0	0.00%	5	0	0.00%
					Yes	2	2	100.00%	13	0	0.00%
			Complex	Pain	No	1	0	0.00%	2	0	0.00%
					Yes	4	4	100.00%	31	16	51.61%

By corroborating all the previous percentage-wise information, as well as the results of the differential statistical analysis equations (chi square $\chi 2$ test with Fisher correspondent), we can conclude that: premenarcheal patients with medium and complex OCLs, from the study group, required surgical intervention; consequently, they are included into the high risk group.

As far as the conservative treatment is concerned, there were 84.6% (n = 44) among the premenarcheal patients and 93.19% (n = 397) among the postmenarcheal patients who benefited from this type of treatment. OCL management of postmenarcheal patients

(representing 87.3% from the total study group), corresponds to the algorithm outlined in the second study. The situation changes for the premenarcheal patients, the conservative treatment being used for 33.3% medium OCLs and 14.3% large OCLs, as compared to 94.7% and 68.7%, respectively, for the medium and large OCLs of postmenarcheal patients.

II.9. General discussions

During the 3 years of study we found an increasing occurrence of OLCs in pediatric patients, but with a significant decreasing trend of incidental findings and, more importantly, of OCL surgical treatment.

In order for the OCL diagnosis not to be overestimated, we would like to highlight the fact that, as this research shows, any cyst smaller than 10 mm, regardless of age, is an ovarian follicle, and that for girls who have already had menarche, an OCL of up to 30 mm is most likely physiological. The present study also took into account 10-30 mm lesions in order to investigate the extent to which they are pathological for a premenarcheal age. However, the results of this thesis showed that even in premenarcheal girls, OCLs smaller than 30 mm did not have a clinical-pathological significance and did not require surgery.

One of the desiderata of this study was the discovery of some risk and prognosis factors for the appearance and evolution of OCL. Of these, the large size, correlated with the complex ultrasound aspect, are well-known to have an unfavourable evolutionary potential. A peculiarity of the studied group was the high incidence of benign neoplasms in the premenarcheal subgroup, which caused the medium (30-49 mm) and complex cystic lesions in this population segment, a risk factor with a surgical therapeutic approach. A risk factor, specific to the socio-economic reality of our region, proved to be the rural area of origin, patients with this feature coming to hospital with large and complicated OCLs, which required surgical treatment, often as a matter of emergency. Comparing our own results with those of other studies, we demonstrated the negative effect of excess weight on the frequency of ovarian cystic lesions, which usually were large or complex OCLs, especially in postmenarcheal patients, but also on the incidence of dysmenorrhea and of menstrual disorders (in particular amenorrhea).

Conservative treatment, as evidenced by this research, should be the first management option for uncomplicated cystic ovarian lesions in pediatric patients, with the mention for patients to urgently go to a physician if symptoms occur. The same attitude of standing in standby can be adopted in the case of a simple OCL, of less than 50 mm, discovered

incidentally intraoperatively. If, however, surgical treatment is required, it should take into account the integrity of the ovary as much as possible, with cystectomy having the best rate of preservation of the ovary. The laparoscopic approach, although recognized as having multiple advantages, is not yet available to any pediatric surgery service in Romania.

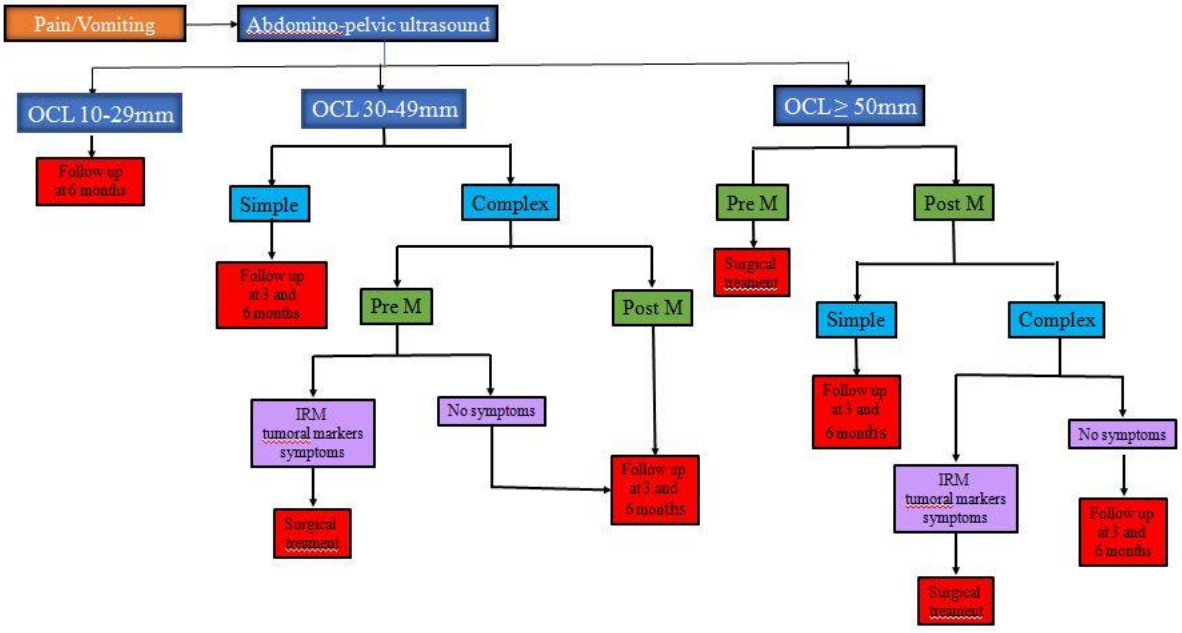
Therapeutic success depends on an early and correct diagnosis, correlated with the patient's menarcheal status, but this can be achieved only in the context of a close interdisciplinary collaboration between the pediatric surgeon and the GP, and with specialists in imaging, pediatrics and endocrinology. In view of optimizing the therapeutic results, we emphasize the fundamental role of the GP in increasing the level of sports, food and health education of the population, in including ovarian pathology in the differential diagnosis of painful abdomen in pediatric patients, and in using the abdominopelvic ultrasound as a mandatory method of first intention in OCL screening.

II.10. General conclusions and the suggested diagnosis and treatment algorithm

- In our study, conducted at the level of Galați county, over a period of three years (2017-2019), the incidence of OCL ≥ 10 mm in girls aged 0-18, was of 14.85%, with the categorical prevalence of postmenarcheal adolescents, and with a peak of incidence at 15 years of age;
- Our research demonstrated that OCLs in pediatric patients are mostly small (10-29 mm), with a simple echographic aspect and right laterality. We also showed that, regardless of age, OCLs smaller than 10 mm are ovarian follicles, and those measuring 10-29 mm may be considered physiological; consequently, the term “cyst” cold be replaced with dominant follicle or follicle in evolution;
- For the patients included in this study, pain, vomiting or a palpable tumour, taken as isolated symptoms, represented alarm factors, but their simultaneous presence in association with large complex OCLs represented an indication for surgical treatment;
- Depending on the presence of pain and on OCL size and aspect, this study conceived a risk score leading to surgical treatment: minimum risk (doesn't require surgery), low risk (2.5% OCLs were surgically treated), medium risk (5-7.5%) and high risk (over 47.5%). For our premenarcheal group, medium and complex OCLs were included in the high risk of surgery group.

- In the present study we proved, by means of statistical tests, that the intraoperative discovery of an OCL < 50 mm, with a simple aspect, allows a conservative approach, with an echographic follow-up of the evolution;
- Our results prove that, except for the cases with diagnosis or suspicion of ovarian malignancy or torsion, all OCLs may be initially treated in a conservative manner, with follow-up at 3 months (the average time for OCL spontaneous disappearance, possibly extended to 6 months), with subsequent evaluation regarding a surgical approach;
- We found significant correlation between the rural area of origin and complicated, surgically treated large, complex OCLs;
- Also, with the help of statistical tests, we confirmed the hypothesis that obesity represents a risk factor for large, complex OCL occurrence, but also for the association of dysmenorrhea and menstrual disorders;
- For our patient group, the ultrasound efficiency was of 93.6% for the diagnosis of OCL, and 75% for the diagnosis of ovarian torsion, which recommends it as an accurate imagistic method for the screening of acute or chronic abdominal pain;
- By corroborating the results obtained during this research, we succeeded in drawing up a diagnostic and treatment algorithm for OCLs occurring at pediatric ages, in accordance with the main symptoms of the patients, their menarcheal status and the OCL ultrasonographic features.

Diagnostic and treatment algorithm (appendix 4)



II.11. Originality and innovative contributions of the thesis

After concluding this research,we consider that we conducted the first study in Romania that includes a large group of patients, with the full spectrum of pediatric ages, and a wide range of OCL sizes, being thus able to assess the incidence of cystic ovarian lesions in Galați County. We also consider that we have proven the importance of the menarcheal status in the evolution and therapeutic decision to be made regarding OCLs.

Moreover, we outlined a surgery risk score, based on the symptomatology, sizes and ultrasound character of the OCL, useful in guiding the therapeutic approach. At the same time, we consider that the research and the establishment of the factors that influence the postoperative rate of ovarian preservation, can guide the choice of surgical technique.

To sum up, we managed to assess the involvement of obesity in the occurrence of OCLs and of menstrual disorders, highlighting the important preventive role that a good health education has.

SELECTIVE REFERENCES

1. Healey A. Embryology of the female reproductive tract. In: Mann GS, Blair JC, Garden AS. (eds). *Imaging of gynecological disorders in infants and children.* Diagnostic Imaging.Berlin: Springer-VerlagBerlin Heidelberg; 2012. p.21-30.
2. Taylor HS, Pal L, Seli E, (eds). *Speroff's Clinical Gynecologic Endocrinology and Infertility*. 9th Edition. Philadelphia: Wolters Kluwer; 2020. Available from: www.academia.edu.
4. Sadler TW. *Langman's Embriologie Medicală*. Ediţia a 10-a. Bucureşti: Editura Medicală Callisto; 2008.
29. Albu I, Georgia R. *Anatomie Topografică*. Ediţia a II-a. Bucureşti: B.I.C. ALL; 1998.
30. Papilian V, Albu I. *Anatomia Omului.* Splanhnologia, volumul II. Ediţia a X-a. Bucureşti: B.I.C. ALL; 2011.
41. Chou CH, Chen MJ. The effect of steroid hormones on ovarian follicle development. *Vitamins and Hormones*. 2018;107: 155-175. Available from: doi: 10.1016/bs.vh.2018.01.013.
44. Broer SL, Broekmans FJ, Laven JS, Fauser BC. Anti-Műllerian hormone: ovarian reserve testing and its potential clinical implications. *Human Reproduction Update Advance Access*. 2014;20(5): 688-701. Available from: doi: 10.1093/humupd/dmu020.
52. Sonmez K, Turkyilmaz Z, Karabulut R, Can Basaklar A. Ovarian masses in infant-juvenile age. *Archivos Argentinos de Pediatría*. 2018;116(3): 359-364. Available from: doi: 10.5546/aap.2018.eng.e356.
61. Zhang M, Jiang W, Li G, Xu C. Ovarian Masses in Children and Adolescents - An Analysis of 521 Clinical Cases. *Journal of Pediatric and Adolescent Gynecology*. 2014;27: 73-77. Available from: doi: 10.1016/j.jpag.2013.07.007.
62. Emeksiz HC, Derinöz O, Akkoyun EB, Güçlü Pınarlı F, Bideci A. Age-Specific Frequencies and Characteristics of Ovarian Cysts in Children and Adolescents. *Journal of Clinical Research in Pediatric Endocrinology*. 2017;9(1): 58-62. Available from doi: 10.4274/jcrpe.3781.
63. Brandt ML, Helmrath MA. Ovarian cysts in infants and children. *Seminars in Pediatric Surgery*. 2005;14: 78-85. Available from: doi:10.1053/j.sempedsurg.2005.01.002.
64. Spinelli C, Di Giacomo M, Cei M, Mucci N. Functional ovarian lesions in children and adolescents: when to remove them. *Gynecological Endocrinology*. 2009;25(5): 294-298. Available from: doi: 10.1080/09513590802530932.

67. Ashwal E, Krissi H, Hiersch L, Less S, Eitan R, Peled Y. Presentation, diagnosis, and treatment of ovarian torsion in premenarchal girls. *Journal of Pediatric and Adolescent Gynecology*. 2015;28(6): 526-529. Available from: doi: 10.1016/j.jpag.2015.03.010.

74. Hermans AJ, Kluivers KB, Wijnen MH, Bulten J, Massuger LF, Coppus SF. Diagnosis and treatment of adnexal masses in children and adolescents. *Obstetrics and Gynecology*. 2015; 125(3): 611-615. Available from: doi: 10.1097/AOG.0000000000000665.

93. Aydin BK, Saka N, Bas F, Yilmaz Y, Haliloglu B, Guran T, et al. Evaluation, treatment and follow-up results of ovarian cysts in childhood and adolescence: a multicenter, retrospective study of 100 patients. *Journal of Pediatric and Adolescent Gynecology*. Available from: doi: 10.1016/j.jpag.2017.01.011.

118. Levine D, Brown DL, Andreotti RF, Benacerraf B, Benson CB, Brewster WR, et al. Management of asymptomatic ovarian and other adnexal cysts imaged at US:Society of Radiologists in Ultrasound consensus conference statement. *Ultrasound Q*.2010;26(3): 121–131. Available from: doi:10.1097/RUQ.0b013e3181f09099.

121. De Silva KS, Kanumakala S, Grover SR, Chow CW, Warne GL. Ovarian lesions in children and adolescents–an 11-year review. *Journal of Pediatric Endocrinology Metabolism*. 2004;17(7): 951-957. Available from: doi: 10.1515/jpem.2004.17.7.951.

146. Kanizsai B, Orley J, Szigetvari I, Doszpod J. Ovarian Cysts in Children and Adolescents: Their Occurrence, Behavior, and Management. *Journal of Pediatric and Adolescent Gynecology*. 1998;11(2): 85-88. Available from: doi: 10.1016/S1083-3188(98)70117-2.

147. Lala SV,Strubel N. Ovarian neoplasms of childhood. *Pediatric Radiology*. 2019;49: 1463–1475. Available from: doi:10.1007/s00247-019-04456-8.

179. Sadeghian N, Sadeghian I, Mirshemirani A, Tabari AK, Ghoroubi J, Gorji FA, et al. Types and frequency of ovarian masses in children over a 10-year period. *Caspian Journal of Internal Medicine*. 2015;6(4): 220-223. Available from: PMID: 26644896.

180. Gupta B, Guleria K, Suneja A, Vaid NB, Rajaram S, Wadhwa N. Adolescent ovarian masses: a retrospective analysis. *Journal of Obstetrics and Gynecology*. 2016;36(4): 515-517. Available from: doi: 10.3109/01443615.2015.1103721.

209. Kirkham Y, Lacy J, Kives S, Allen L. Characteristics and management of adnexal masses in a canadian pediatric and adolescent population. *Journal of Obstetrics and Gynaecology Canada*. 2011; 33(9): 935–943. Available from: doi: 10.1016/s1701-2163(16)35019-8.

251. Gilligan LA, Trout AT, Schuster JG, Schwartz BI, Breech LL, Zhang B, et al. Normative values for ultrasound measurements of the female pelvic organs throughout childhood and adolescence. *Pediatric Radiology*. 2019;49(8): 1042-1050. Available from: doi: 10.1007/s00247-019-04419-z.

254. Caprio MG, Di Serafino M, De Feo A, Guerriero E, Perillo T, Barbuto L, et al. Ultrasonographic and multimodal imaging of pediatric genital female diseases. *Journal of Ultrasound*. 2019;22(3): 273-289. Available from: doi: 10.1007/s40477-019-00358-5.

256. Paltiel HJ, Phelps A. US of the pediatric female pelvis. *Radiology*. 2014;270(3): 644–657. Available from: doi: 10.1148/radiol.13121724.

272. User İR, Karakuş SC, Özokutan BH, Akçaer V, Burulday B, Ceylana H. Can preoperative findings help to interpret neoplastic and non-neoplastic lesions of ovary and affect surgical decisions in children and adolescents?. *Archivos Argentinos de Pediatria*. 2019;117(5): 294-400. Available from: doi: 10.5546/aap.2019.eng.294.

282. Bonde AA, Korngold EK, Foster BR, Fung AW, Sohaey R, Pettersson DR, et al. Radiological appearances of corpus luteum cysts and their imaging mimics. *Abdominal Radiology (NY).* 2016;41(11): 2270-2282. Available from: doi: 10.1007/s00261-016-0780-1.

331. Bergeron LM, Bishop KC, Hoefgen HR, Abraham MS, Tutlam NT, MerrittDF, et al. Surgical Management of Benign Adnexal Masses in the Pediatric/Adolescent Population: An 11-Year Review. *Journal of Pediatric and Adolescent Gynecology*. 2017 Feb;30(1): 123-127. Available from: doi: 10.1016/j.jpag.2016.09.002.

332. Dural O, Yasa C, Bastu E, Ugurlucan FG, Yilmaz G, Yuksel B, et al. Laparoscopic Outcomes of Adnexal Surgery in Older Children and Adolescents. *Journal of Pediatric and Adolescent Gynecology*. 2016;29(2): 182-183. Available from: doi: 10.1016/j.jpag.2016.01.059.

333. Ritchie J, O'Mahony F, Garden A. Guideline for the management of ovarian cysts in children and adolescents. *The British Society for Paediatric & Adolescent Gynaecology*. 2017. Available from: britspag.org.

340. Tessiatore P, Guanà R, Mussa A, Lonati L, Sberveglieri M, Ferrero L, et al. When to operate on ovarian cysts in children ?.*Journal of Pediatric Endocrinology and Metabolism*. 2012;25(5-6): 427-433. Available from: doi: 10.1515/jpem-2012-0049.

363. Shazly SA, Badee AY, Ali MK, Sobh AM, Aleem AA.The laterality of ovulation: how far does it matter?. *European Journal of Obstetrics, Gynecology and Reproductive Biology*. 2013;167(1): 8-13. Available from: doi: 10.1016/j.ejogrb.2012.10.018.

383. Stefanopol IA, Tiron Z, Neagu AI, Pavel LL, Sarbu V, Dragomir-ananie ET. Diagnostic and treatment of ovarian cystic lesions in premenarheal girls: a 3-years study. *Revista de Chimie*. Volume: 71, Year: 2020;71(2): 460-465. Available from: doi.org/10.37358/RC.20.2.7950.