

Factors Associated With Ovarian Preservation in Children and Adolescents With Primary Tumors of Ovary

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Objective: To determine management of pediatric ovarian masses and identify the factors associated with ovarian preservation. **Methods:** From January, 2002 to January, 2019 the case records of 72 patients (median age 14 y), who underwent surgery for ovarian tumors were retrospectively reviewed. **Results:** Tumors were most common in the age group 14-17 yrs (58.3%) and most (91.7%) were benign. The most common presenting symptom was abdominal pain (80.5%) followed by vomiting, elevated body temperature, nausea and palpable abdominal mass. 25 (34.7%) patients had an ovarian torsion. Six out of 72 (8.3%) patients had malignant tumors. Of the patients with malignant tumors, 75% had abnormal alpha-fetoprotein and 50% had abnormal β -human chorionic gonadotropin levels ($P < 0.001$). Ovarian-preserving surgery was successfully performed in 74.3% of the benign lesions and two patients (25%) with malignant tumors ($P = 0.004$). **Conclusions:** Factors associated with ovarian-preserving surgery are benign tumor, normal tumor markers levels, and smaller size of tumor.

Keywords: Adnexal mass, Laparoscopy, Management, Ovariectomy.

Ovarian tumors requiring surgical intervention are uncommon in children and adolescents [1]. The incidence of ovarian tumors in pediatric population is 2.6:100 000 girls per year, with higher rates in adolescents [2]. Only about 10-20% of all ovarian tumors in children and adolescents are malignant and comprises approximately 1-2% of all childhood malignancies [1-3]. Germ-cell tumors are the most common ovarian tumors in childhood and adolescence with mature cystic teratomas accounting for 55-70% of cases [4]. The presence of an ovarian tumor in children is a diagnostic and therapeutic challenge. The signs and symptoms can mimic many abdomino-pelvic medical or surgical diseases [2]. Ovarian-conserving procedures have proven safe for children and adolescents. Over the past decade, minimally invasive surgical techniques have become the standard of care for removing benign ovarian tumors because of shorter recovery time, decreased pain, and improved cosmesis [5,6].

The aim of this study was to determine the epidemiological, demographic and clinical characteristics and the management of pediatric ovarian tumors. Secondary aim was to identify the factors that are associated with ovarian preservation.

METHODS

The case records of all children and adolescents (age 0-17 y) who underwent surgery for ovarian tumors between January, 2002 and January, 2019 in the Department of pediatric surgery, at University hospital of Split, Croatia, were retrospectively reviewed. The study was approved by the ethics committee of our hospital. Exclusion criteria were: patients with incomplete documentation and the patients where another pathological cause was found during surgical exploration. The following parameters were recorded for each patient: demographic data, presenting symptoms, lateralization of tumor, serum tumor markers, physical examination, surgical findings, tumor size, pathohistological analysis, length of hospitalization and complications. Regarding type of tumor patients were divided into two groups of benign and malignant tumors. The study population was also stratified into 4 subgroups on the basis of patient age: Group I included antenatal and newborn patients; Group II included patients age 1-8 years; Group III included patients age 8-13 years; and Group IV patients age 14-17 years.

The data were analyzed using the SPSS 24.0 (IBM Corp, Armonk, NY) software program. Differences in quantitative variables between the groups were tested

with Mann-Whitney U test. The Chi-square test was used for comparing categorical data. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 72 female patients (6 with bilateral tumors), with median age of 14 (IQR 8.5, 16) years and median BMI of 22.5 (IQR 18, 25) kg/m², underwent surgery because of ovarian tumors. Eight patients (11.1%) were diagnosed during the antenatal or newborn period, two (2.8%) at ages 1-7, 20 (27.8%) at prepubertal ages; and 42 (58.3%) patients were identified after the age of 14 years. From total number of patients, 46 (63.8%) patients underwent emergent surgery because of the suspicion of ovarian torsion. The other 26 (36.2%) patients underwent elective surgery. The most common presenting symptom was abdominal pain (80.6%) followed by vomiting (26.4%), palpable abdominal mass (9.7%), elevated body temperature (9.7%), nausea (9.7%), inappetence (6.9%), vaginal bleeding (2.8%), amenorrhea (2.8%), dysuria (2.8%) and pubertas praecox (1.4%). Ten patients were asymptomatic (13.9%). Clinical and demographic data are presented in **Table I**. The median tumor diameter was 9.4 cm (IQR 7.5, 14). However, there was a significant difference in tumor size between patients who had benign neoplasm and those with malignant tumors ($P < 0.001$). A laparoscopic resection was performed in 43 (59.7%) and open procedure in 29 (40.3%) patients. Ovarian-preserving surgery was successfully performed in 74.3% of the benign tumors versus 25% with malignant tumors

($P = 0.004$). Regarding the patients with malignant tumors who underwent ovary sparing surgery, one patient has been diagnosed as dermoid cyst by radiologist with no abdominal lymphadenopathy and with negative tumor markers and on pathology immature teratoma was found. Another patient was girl with juvenile type granulosa cell tumor, which was considered as tumor with low malignant potential so we decided to perform ovarian sparing tumor resection. Both patient had uneventful recovery and at follow up after five years both were completely symptom free and without signs of tumor at magnetic resonance imaging.

Two (2.8%) patients with benign tumor (one mature teratoma and one simple ovarian cyst) had elevated level of alpha-fetoprotein (AFP). Of the patients with malignant tumors, 75% (five patients with dysgerminoma and a patient with yolk sack tumor) had abnormal AFP levels and 50% (three patients with dysgerminoma and a patient with yolk sack tumor) had abnormal b-human chorionic gonadotropin (b-HCG) levels ($P < 0.001$). Outcome of treatment of all patients are presented in **Table II**. Regarding complications after surgery in one case of mature teratoma residual tumor was found at MR at 1 year follow up. In that case redo surgery was performed. In three cases (one granulosa cell tumor and two ovarian cysts) postoperative bleeding was recorded. In all three cases bleeding stops spontaneously and hematoma was managed conservatively. Ovarian torsion was detected in 25 patients; oophorectomy was reserved for 13 (52%) gangrenous ovaries. Of all ovarian tumors, 50 (64.1%) were non-neoplastic lesions (cysts), 20

Table I Baseline Characteristics of Children with Ovarian Tumors (N=72)

Parameters	Benign	Malignant
#Age, y	13.5 (8.5, 15.5)	14 (11, 16)
Age group, y		
0-1	7 (10.6)	1 (16.7)
2-7	2 (3)	0
8-13	18 (27.3)	2 (33.3)
14-17	39 (59.1)	3 (50)
Lateralization		
Left	20 (30.3)	2 (33.3)
Right	42 (63.6)	2 (33.3)
Bilateral	4 (6.1)	2 (33.3)
*# Tumor diameter, cm	7.5 (5.5, 10)	13.0 (10.5, 17)
*Tumor markers (α -FP; β -HCG)		
Positive	2 (2.8)	6 (75)
Negative	70 (97.2)	2 (25)

All values in no. (%) except #median (IQR); * $P < 0.001$.

Table II Treatment Outcomes of Patients (0-17 y) with Ovarian Tumors (N=72)

Parameters	Benign	Malignant
Surgical approach		
Open surgery	25 (37.9)	4 (66.7)
Laparoscopic surgery	41 (62.1)	2 (33.3)
*Procedure		
Ovarian-preserving surgery	52 (74.2)	2 (25)
Ovariectomy	18 (25.8)	6 (75)
Ovarian torsion		
Ovarian-preserving surgery	11 (47.8)	1 (50)
Oophorectomy	12 (52.2)	1 (50)
Complications		
Bleeding	2 (2.8)	1 (12.5)
Residual tumor mass	1 (1.4)	0
#Hospital stay	3 (2, 4)	4 (2, 6)

All values in no. (%) except #median (IQR); * $P = 0.004$.

(25.6%) were benign tumors, and 8 (10.3%) were malignant tumors (**Table III**). Regarding the patients with bilateral ovarian tumors in one case final diagnosis was bilateral dysgerminoma, two cases of bilateral matured teratoma, one case of simple ovarian cyst and matured teratoma, and two cases of bilateral simple ovarian cysts.

DISCUSSION

The results of this study showed that the risk factors for ovariectomy are a malignant pathology, elevated levels of serum tumor markers and large tumor size. Surgical management of ovarian tumors in children should be based on ovarian-preserving surgery. Most of the tumors were benign and found in prepubertal and adolescent age groups. Laparoscopy may be safe and effective method for ovarian-preserving surgery in patients with ovarian cysts and benign ovarian tumors, with abdominal pain as the most common presenting symptom. Apart from the tumor, pain may also indicate ovarian torsion, especially if accompanied by vomiting and nausea.

Retrospective character is the main limitation of this study. Also, due to low incidence of ovarian tumors in this age group, there is a relatively small number of patients included in the study, so further studies are needed to analyze the same parameters on a larger sample.

Among pediatric patients undergoing surgery for ovarian tumors, the incidence of malignancy ranges from 4 to 20% [2,3,7]. Rate of malignant tumors in this

research was 10.8%, which is in accordance with previous studies [8-10]. The most common tumors in this study were germ cell tumors. Similar data were reported in other studies [10]. Dysgerminoma was the most common malignant tumor in this study similar to other published studies [11]. The most common presenting symptom of ovarian tumors is abdominal pain, which is in accordance with our study [2,4,6,8-10]. Abdominal distension and vomiting are less frequent presenting symptoms [9,10]. Malignant tumors in this study had a diameter greater than 9 cm (median 13 cm) with no difference in the age of presentation between patients who had benign tumors and those who had malignant tumors. Similar findings were confirmed in other published studies [2]. Taskinen, *et al.* [12] reported that malignant high-grade tumors were detected only in girls older than 9 years. Over the past decade, minimally invasive surgical techniques have become the standard of care for removing benign adnexal masses and many pediatric surgeons prefer laparoscopy because of shorter recovery time, decreased pain, and improved cosmesis [13-15]. Rogers, *et al.* [15] concluded that it is safe in children and adolescents to proceed with a laparoscopic approach for adnexal masses without complex features measuring less than or equal to 8 cm in maximum diameter [15]. In present study we also removed successfully cysts and teratomas larger than 8 cm. If there is a surgical indication, surgery must conform to oncologic standards and must be as conservative as possible to preserve future fertility [2,13,14]. In present study, higher oophorectomy rate was found in children with a tumor size greater than 6.5 cm. The tumor size was significantly larger in the patients who underwent oophorectomy than in those who underwent ovarian-preserving surgery. Similar findings were reported in literature [2,4]. The most common reason for oophorectomy, except malignancy, was torsion of the ovary with gangrene of the ovarian tissue. Ovarian-conserving procedures has proven safe for adolescents and over the last decade minimally invasive surgical techniques have become the gold-standard treatment. Many surgeons agree that ovary-sparing surgery should be attempted whenever possible for ovarian tumors in pediatric patients [2,4,11-15]. In all our cases when there was possibility to remove tumor, safe ovarian-sparing surgery was performed. Ovarian torsion is a true emergency that always have to be considered in the differential diagnosis of any pediatric female patient presenting with acute abdominal pain. Recently, it has been proven that the black-bluish macroscopic appearance of the ovary is not a true indication of the degree of ischemia and that there is no valid clinical method of predicting the viability of the twisted ovary [2,16]. In our study AFP and β -HCG were highly

Table III Histopathology of Ovarian Tumors in Children (N=78)

<i>Histopathological type</i>	<i>No. (%)</i>
<i>Germ cell tumors</i>	22 (28.2)
Mature (dermoid) teratoma	15 (19.2)
Immature teratoma	1 (1.3)
Dysgerminoma	5 (6.4)
Yolk sac tumor	1 (1.3)
<i>Specialized stromal ovarian tumors*</i>	1 (1.3)
<i>Epithelial tumors</i>	5 (6.4)
Serous cystadenoma	3 (3.8)
Cystadenofibroma	1 (1.3)
Mucinous cystadenoma	1 (1.3)
<i>Ovarian cysts</i>	50 (64.1)
Simple cyst	25 (32.1)
Follicular cyst	9 (11.5)
Corpus luteum cyst	11 (14.1)
Paraovarian cyst	5 (6.4)

*All value in no. (%); 6 patients had bilateral tumors; *granulosa cell tumor (juvenile type).*

WHAT THIS STUDY ADDS?

Risk factors for ovariectomy are a large tumor, malignant pathology, and elevated levels of tumor markers.

associated with malignancy. All patients with ovarian cysts had normal levels of serum tumor markers. Two patients with benign tumor had elevated level of AFP. Papic, *et al* [17], reported also that that AFP and β -HCG were highly associated with malignancy, and no benign tumors were positive for these markers in their study. However, other reports showed that the rate of benign lesions associated with the rise of tumor markers varies from 3% to 20% [2,16].

In conclusion, ovarian tumors in childhood are mostly benign. The most common presenting symptom of ovarian tumors in children is pain. The risk factors for oophorectomy were a malignant pathology, elevated levels of serum tumor markers and large tumor size. Surgical management of ovarian masses in children should be based on ovarian-preserving surgery whenever it is possible.

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