

# Pediatric Ovarian Tumors: A Review of 67 Cases

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**Background.** Ovarian tumors are uncommon but important childhood neoplasms. **Procedure.** We reviewed records of 67 pediatric patients presenting to three pediatric referral centers from 1980 to 2003. **Results.** Thirty patients had benign tumors. Thirty-seven patients had malignant tumors: 11 immature teratomas, seven malignant mixed germ cell tumors, seven juvenile granulosa cell tumors, five dysgerminomas, two endodermal sinus tumors, two serous papillary cystadenocarcinomas, one small cell carcinoma, one anaplastic sex-cord tumor, and one undifferentiated sarcoma. More than half presented with abdominal pain. Forty-six percent had an abdominal mass at the time of presentation. Other signs and symptoms included poor appetite (15%), urinary symptoms/urinary infection (9%), menstrual changes (9%),

and weight loss (6%). Precocious puberty was noted in seven patients. Torsion was seen more often in patients with benign tumors (23 vs. 8%); two patients had both torsion and acute appendicitis. The neoplasm was an incidental finding in 12 patients. **Conclusions.** Fifty-five percent of the 67 ovarian tumors presenting to our centers were malignant. Pain was the most common symptom, although presence of an abdominal mass was frequent, and other symptoms non-specific. Almost all neoplasms presented as unilateral masses and rarely were metastatic at diagnosis. Ovarian tumors must be considered in the differential diagnosis of young girls with abdominal pain, mass, or other non-specific symptoms. *Pediatr Blood Cancer* 2005; 44:167–173. © 2004 Wiley-Liss, Inc.

**Key words:** dysgerminomas; epithelial tumors; germ cell tumors; granulosa cell tumors; ovarian neoplasms; precocious puberty

## INTRODUCTION

Pediatric ovarian tumors are an uncommon but important form of childhood cancer. Ovarian tumors are the most frequent neoplasms of the female genital tract in childhood [1] and are generally considered to account for approximately 1% of all malignancies in patients ages 0–17 years [2]. Ovarian masses include neoplastic and non-neoplastic processes. Non-neoplastic conditions include follicular cysts, corpus luteal cysts, and endometriomas. Neoplastic processes include both benign tumors such as mature cystic teratomas as well as highly malignant tumors. In addition, there are tumors of low malignant potential that frequently follow a benign clinical course.

Various classification and nomenclature systems have been developed to describe the spectrum of ovarian tumors. Generally these tumors are classified into three main categories including epithelial, stromal, and germ cell tumors.

Previous studies of pediatric ovarian tumors in children have noted a predominance of germ cell tumors. This is in contrast to the adult literature, which notes the predominance of tumors of epithelial cell origin [3]. This difference highlights the importance of considering patient age when evaluating ovarian pathology.

Germ cell tumors include teratomas and gonadoblastomas as well as endodermal sinus tumors, also called yolk sac tumors, embryonal carcinomas, polyembryomas, and choriocarcinomas. Teratomas include both immature

(malignant) and mature (benign) forms. Immature teratomas are classified according to their level of differentiation [4]. Histologic level of differentiation determines the level of malignancy. Gonadoblastomas occur exclusively in patients with dysgenetic gonads and are classified as benign tumors, however, malignant dysgerminomas are frequently found within these tumors.

Children may also present with non-germ cell tumors including sex cord-stromal tumors and epithelial tumors. Sex cord stromal tumors include thecoma–fibroma, Sertoli–Leydig cell tumors and granulosa cell tumors. Juvenile granulosa cell tumors follow a very different clinical course than granulosa cell tumors in adult women and although they have malignant potential, they commonly follow a benign clinical course.

Epithelial tumors, including cystadenoma in benign, borderline, and malignant forms, are common in adult women, though much less frequent in children. Small cell

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carcinomas of the ovary occur very rarely, though this tumor has been reported in children as young as 14 months [5]. These tumors usually are found at an advanced stage and are generally considered to have a poor prognosis. This study summarizes all ovarian tumors diagnosed at three pediatric referral centers in recent years.

## MATERIALS AND METHODS

We identified 67 patients ages newborn to 18 years presenting to the University of Minnesota and Children's Hospitals of Minneapolis and Saint Paul from 1980 to 2003. All three hospitals are considered referral centers for pediatric oncology care.

Case records were obtained by searching tumor registries at the participating hospitals as well as by searching medical records information via ICD-9 codes. All available medical records were reviewed. Only those patients with primary ovarian tumors were considered. Patients with metastasis to the ovary were excluded. Non-neoplastic processes such as simple cysts were also excluded from this review. This review follows the WHO pathohistological classification of ovarian tumors (WHO, 1973) and International Federation of Gynecology and Obstetrics (FIGO) staging criteria.

## RESULTS

### Age

Only one patient presented in infancy (Figs. 1 and 2). In children less than 6 years of age, malignant tumors were more common than benign tumors. Nearly half of all malignant tumors were in children ages 7–12 years. Mature teratomas were more common in adolescence.

### Chromosomal Abnormalities

Constitutional chromosomal analysis revealed: del (10q23) in a patient with grade IV stage IV mixed germ cell tumor; trisomy (XXX) in a patient with mixed germ

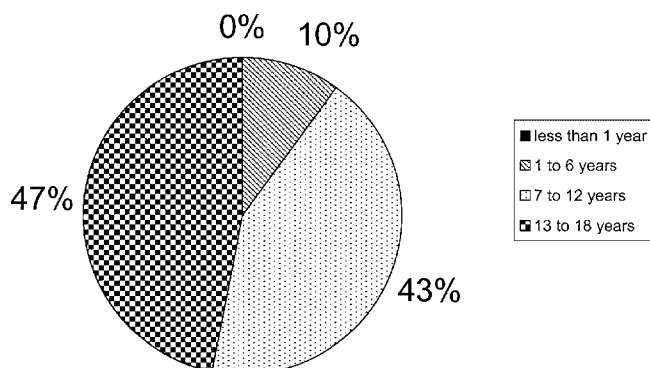


Fig. 1. Age at diagnosis of benign tumors.

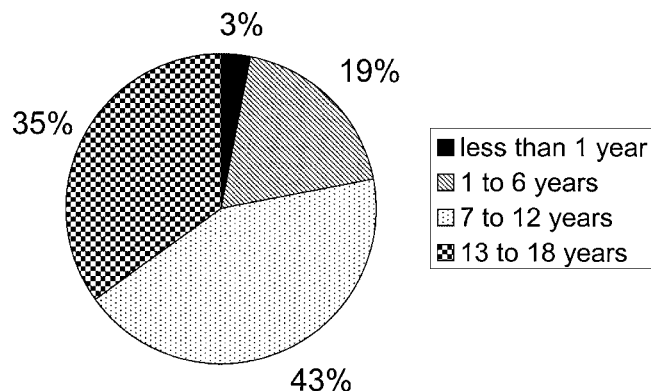


Fig. 2. Age at diagnosis of malignant tumors including juvenile granulosa cell tumors.

cell tumor; 46,XY in a phenotypic female with dysgerminoma; 46,XY in a hermaphrodite with stage IA dysgerminoma; 45,XO/46X psu dic Y in a patient with Turner syndrome and bilateral gonadoblastoma with unilateral dysgerminoma.

### Signs and Symptoms at Presentation

More than half of our patients presented with abdominal pain as the primary symptom (Fig. 3). Forty-six percent presented with abdominal mass. Torsion was frequently seen (17%). Two patients, both with benign cystic teratomas, had both pathologically confirmed torsion and acute appendicitis at the time of surgery. Twelve patients (18%) were asymptomatic at the time of diagnosis and the neoplasm was found either during a routine health care visit or during radiographic screening for another medical condition.

There was little difference in the clinical presentation of children with benign versus malignant tumors. However, patients with benign masses, particularly mature cystic teratoma, were more likely to present with torsion (23 vs. 8%). Precocity was most common in children with juvenile granulosa cell tumor (five of seven patients). Overall, 93% (n = 62) of tumors were unilateral; 58% were right-sided. Bilateral tumors included bilateral gonadoblastoma with unilateral dysgerminoma, bilateral papillary serous adenocarcinoma, bilateral mucinous cystadenoma, and bilateral mature teratomas. Contralateral ovarian findings included mature cystic teratoma, lymphangioma, and simple cysts.

### Diagnostic Studies

Abdominal radiograph, abdominal ultrasound and computed tomography were frequently performed (see Table I). Three patients underwent exploratory laparotomy prior to any imaging study due to a presumed diagnosis of acute abdomen.

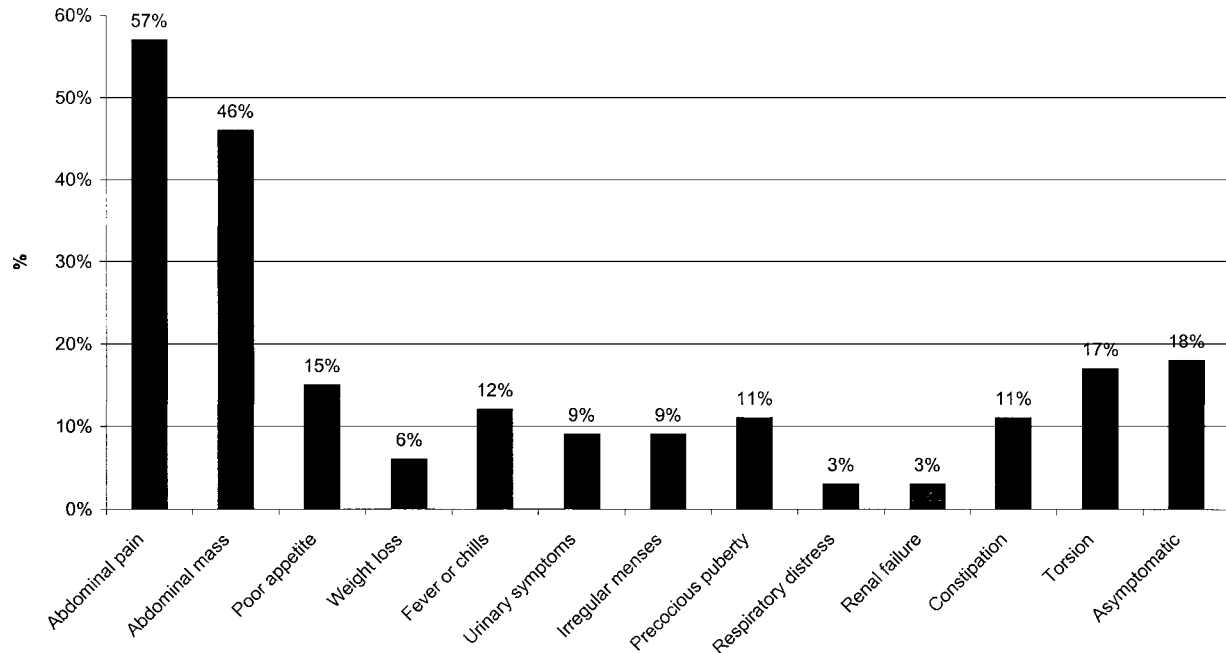


Fig. 3. Signs and symptoms at presentation.

## Diagnoses

The most common benign tumors were cystic teratomas. Cystadenomas were also noted, one with borderline features (see Tables II and III).

Of the malignant tumors, immature teratomas were the most common. Seven patients had juvenile granulosa cell tumors; these were often associated with precocious puberty. Seven patients were diagnosed with mixed malignant germ cell tumors. Five patients had dysgerminomas; two of these were otherwise healthy and had normal chromosomes. Two patients had endodermal sinus tumors, each with a palpable pelvic mass at the time of presentation. One patient had unilateral endodermal sinus tumor with a contralateral mature cystic teratoma. Other malignancies observed included small cell carcinoma, cystadenocarcinoma, papillary adenocarcinoma, undifferentiated sarcoma, and anaplastic sex cord tumor with Sertoli-Leydig and granulosa-theca cell forms.

TABLE I. Studies Performed to Establish Diagnosis

Initial diagnostic studies	%
Abdominal radiograph	33
Abdominal ultrasound, no CT	30
Abdominal CT, no ultrasound	30
Both CT and ultrasound	20
Magnetic resonance imaging	5
Exploratory lap prior to imaging	4

CT, computed tomography; lap, laparotomy.

Abdominal radiographs were frequently performed in addition to other studies.

## Tumor Markers

Patients with benign cystic teratomas had AFP, CEA and  $\beta$ -hcg in the normal range, however, LDH and ESR were often elevated. Patients with juvenile granulosa cell tumors and precocious puberty often had normal AFP,  $\beta$ -hcg and CEA, however, estradiol, and testosterone were frequently elevated. One patient with a juvenile granulosa cell tumor had increased AFP and inhibin with a normal  $\beta$ -hcg and CEA.

Elevated tumor markers seen in immature teratomas included increased AFP, LDH, and CA-125. AFP was elevated in 10 of our 11 cases. CA-125 was measured in only two cases of immature teratoma and was found to be elevated in both.  $\beta$ -hcg was normal in all but one case where it was found to be minimally elevated and resolved following treatment. Both patients with endodermal sinus tumors had elevated AFP levels. One also had elevated CA-125 and LDH.  $\beta$ -hcg was normal in each case.

All tumor markers were negative in patients with papillary serous cystadenocarcinoma and undifferentiated sarcoma. A patient with small cell carcinoma presented with marked hypercalcemia and was the only patient in our study to have hypercalcemia at the time of presentation. One patient diagnosed with an anaplastic sex cord tumor was found to have an elevated CA-125.

Tumor marker elevation in mixed malignant germ cell tumors depended heavily on the tissue components present. One patient with precocious puberty was found to have a mixed germ cell tumor with marked elevation of AFP,  $\beta$ -hcg, DHEAS, and testosterone. Mixed

TABLE II. Characteristics of Patients With Benign Tumors

Diagnosis	%	N	Age range (y)	Mean age (y)	Associated medical conditions
Cystic teratoma	35.8	24	4–17	11.5	Tuberous sclerosis Hodgkins disease
Cystadenoma	9.0	6	11–17	14	Gastroschisis with short bowel syndrome Congenital lumbosacral myelomeningocele

y, year(s).

TABLE III. Characteristics of Patients With Malignancies

Diagnosis	%	N	Stage/grade	Treatment/outcome	Age at dx	Associated medical conditions
Immature teratoma	16.4	3	Stage IA, grade I	Resection, NED	10–16 y	
		3	Stage IA, grade II	Resection, NED	11–16 y	
		3	Stage IA, grade II–III	Two resection, one resection and chemo, NED	9–11 y	
		1	Stage IC, grade II	Resection, chemo, NED at 4 y F/U	12 y	
		1	Stage IV, grade III	Resection, chemo, NED at 12 y F/U	2 y	
Dysgerminoma	7.4	1	Stage IA	Bilateral oophorectomy, NED at 4 y F/U	7 y	46,XY
		1	Stage IA	Bilateral oophorectomy,*	14 y	XO with XY mosaicism
		1	Stage IA	Resection, recurrence at 2 y, curr chemo	18 y	Cystic fibrosis
		1	Stage IA	Resection, chemo, NED at 9 y F/U	7 y	Healthy, 46,XX
		1	Stage IA	Bilateral oophorectomy, recurr, resection, chemo,*	12 y	46,XY
Endodermal sinus tumor	3.0	1	Stage IA	Resection, chemo, NED at 5 y F/U	15 y	
		1	Stage IA	Resection, chemo, NED at 1 y F/U	16 y	
Juvenile granulosa cell tumor	10.5	5	Stage I	Resection, NED at 1–4 y F/U	1–8 y	Precocious puberty at dx
		1	Stage I	Resection, NED at 1 y F/U	6 y	Estrogen hepatopathy at dx
		1	Stage I	Resection, NED at 1 y	5 mo	Ascites, respiratory distress at dx
Mixed germ cell tumor	10.5	1	Stage I	Resection, chemo, recurrence,*	7 y	AVM, deafness, precocious puberty
		1	Stage I	Resection, recurr, resection, chemo, recurrence,*	3 y	
		1	Stage II	Resection, chemo NED at 11 y F/U	13 y	
		1	Stage II	Resection, chemo, NED at last F/U	6 y	47,XXX
		1	Stage III	Resection, chemo, NED at 6 y F/U	16 y	Family history of ovarian cancer
		1	Stage IIIC	Resection, chemo, NED at 2 y F/U	14 y	Factor V Leiden heterozygote
		1	Stage IV	Resection, chemo, resection, chemo, NED at 2 y F/U	9 y	10q23 deletion
Small cell carcinoma	1.5	1	Stage III	Resection, chemo/XRT, autoBMT, NED at 5 y F/U	12 y	Hypercalcemia at diagnosis
Cystadenocarcinoma	1.5	1	Unstageable	Resection,*	18 y	Werdnig–Hoffman disease
Papillary adenocarcinoma	1.5	1	Stage IIc, grade I	Resection, chemo, persistent disease, chemo, died	16 y	
Undifferentiated sarcoma	1.5	1	Stage I	Resection, chemo, remission, second tumor (see text)	10 y	Duplicated renal collecting system
Anaplastic sex cord tumor+	1.5	1	Unstageable	Resection, chemo, recurrence, autoBMT, died	14 y	Family history of ovarian cancer

y, year(s); NED, no evidence of disease; \*, outcome unknown; F/U, follow-up; dx, diagnosis; chemo, chemotherapy; AVM, arteriovenous malformation; autoBMT, autologous bone marrow transplant; +, Sertoli–Leydig and granulosa-theca cell forms.

germ cell tumors including endodermal sinus tumor components were associated with elevated AFP. For all tumors, abnormal lab values normalized following treatment and in two cases tumor marker elevation helped to diagnose recurrence.

### Therapy

Treatment of benign tumors was largely surgical. Five patients were treated with cystectomy alone. Twenty-two patients underwent unilateral salpingo-oophorectomy. Three patients underwent unilateral salpingo-oophorectomy with biopsy or cystectomy of the contralateral ovary. Eight patients also underwent appendectomy; two of these patients had histological findings consistent with appendicitis.

Even with malignant tumors, conservative therapy was more common than radical resection, likely due to the ages and diagnoses of the patients studied. Unilateral salpingo-oophorectomy was the most common procedure. Bilateral salpingo-oophorectomy was performed in one patient with stage IIIC papillary serous adenocarcinoma and in patients with dysgerminoma in the setting of chromosomal abnormalities predisposing to malignancy. One patient with stage IV mixed germ cell tumor underwent radical resection following initial chemotherapy. Peritoneal fluid sampling, lymph node dissection, and partial omentectomy were frequently performed. Small bowel resection was required in one case.

### Metastasis

Metastasis was rarely noted at the time of diagnosis (Table IV). Peritoneal gliomatosis was seen in two patients, both with immature teratomas. Three patients eventually relapsed despite having no initial evidence of metastatic disease.

**TABLE IV. Frequency and Timing of Metastasis to Various Sites**

Timing of metastasis	N	Location
At time of diagnosis	6	Total patients
	2	Peritoneal fluid
	2	Lymph nodes
	1	Lung
	1	Intestine
	1	Uterine serosa
	1	Diaphragm
	2	Peritoneal gliomatosis
After initial therapy	3	Total patients
	1	Lymph nodes
	1	Liver and omentum
	1	Rectal wall

Although only six patients were noted to have metastases at the time of diagnosis, some patients had metastases to more than one site.

**TABLE V. Complications Seen Following Therapy**

Complications	N
Febrile neutropenia	9
Wound infection	3
Decreased pulmonary function	2
Hemorrhagic cystitis	1
Sensorineural hearing loss	1
Peripheral neuropathy	1
Persistent abdominal pain	1
Pneumomediastinum	1
ARDS	1
Post-operative vaginal bleeding	1
Premature ovarian failure	1

ARDS, acute respiratory distress syndrome.

### Complications

Few complications were seen in our patients (Table V). Post-operative vaginal bleeding was observed in one patient following resection of her juvenile granulosa cell tumor with sexual precocity. Side effects of chemotherapy, including neutropenic fever and infection as well as drug-specific complications, occurred. Little information on eventual fertility is available for the patients in our study given their young age and recent diagnoses. One patient is noted to have premature ovarian failure by chart records, although the eventual rate of ovarian failure will likely be higher.

### Second Tumors

One patient treated with surgical resection and chemotherapy for an undifferentiated sarcoma of one ovary was later found to have virilization and a Sertoli–Leydig cell tumor of the contralateral ovary. This patient has normal chromosomes and was the only patient in our study to develop a second ovarian malignancy.

### DISCUSSION

We reviewed modern experience with ovarian tumors in children and adolescents and found a malignancy rate of 55%, slightly higher than previously observed. Reported rates of malignancy vary by study. Some studies have included simple cysts and torsional cysts as part of analyses of ovarian masses [6–9] while some have included only neoplastic conditions [10–12]. Classification of borderline or premalignant tumors varies between studies as well. Some studies have included juvenile granulosa cell tumors in the malignant category [7,8,10–12] while others have classified them as benign [6].

Several factors may have led to an overestimation of our rates of malignancy: first, all three hospitals analyzed in this study are referral centers. Each facility has several pediatric oncologists on staff. Also, our search methods (OncoLog and Cancer Data Services) may tend to include more patients with malignant disease. Patients with benign

disease were identified using ICD-9 codes, which may have missed some cases.

Skinner et al. [11] reported a rate of malignancy among neoplasms of 41.4%. This study was a retrospective review of 29 cases in a pediatric referral center in Indianapolis. This study found 12 benign teratomas, three malignant germ cell tumors, two immature teratomas, three granulosa-theca tumors, two Sertoli-Leydig cell tumors, two lymphomas, and one each of mucinous cystadenoma, cystadenocarcinoma, small cell carcinoma, fibroma and hemangioma. Hassan et al. [1] in Athens reviewed 57 cases of ovarian tumors in girls though age 19. In this review, 77.2% of cases were benign. Malignancies constituted nearly 16% and the remainder were borderline. In their study, mature cystic teratoma was the most frequent diagnosis and germ cell tumors comprised 44.5% of all malignant tumors. Freud et al. [7] reviewed 34 ovarian masses in Tel Aviv in girls from birth to 17 years. Their review found 18 non-neoplastic processes and 16 neoplasms of which 50% were malignant.

Imai et al. [12] analyzed 114 children less than 18 years of age who were diagnosed with ovarian tumors. In their review, 75% were benign, 20% malignant, and 5% potentially malignant. Of all tumors, 55 were of germ cell origin and 33 of epithelial origin. Eighteen tumors were of stromal origin. In a study by Brown et al. [6], 91 cases were reviewed; this included simple cysts and torsion-related cysts, which may account for the low rate of malignancy (18/91). In their study, ultrasound was 100% accurate in diagnosing the process as occurring in the ovaries, however, ultrasound was not able to distinguish benign from malignant neoplasms. Among neoplastic masses in their study, the risk of malignancy for patients less than 8 years was only 3% though this risk increased to 33% in patients 9 years and older [6].

In our study, juvenile granulosa cell tumors were classified as malignant due to their malignant potential, though all of the cases in our series behaved in a clinically benign fashion. Each of the seven patients with juvenile granulosa cell tumors in our study was treated with either unilateral oophorectomy or unilateral salpingo-oophorectomy. None had chemotherapy. None have evidence of recurrence at this time. Although our patients did not develop metastasis or recurrence, Calaminus et al. [13] noted eight children with stage IC juvenile granulosa cell tumors, four patients with stage IIC, and one patient with stage IIIC disease. Adjuvant chemotherapy was used for eight of these patients and additionally for one patient in stage IA whose pathologic diagnosis included a high mitotic index. During a follow-up period of 168 months, they noted an event-free survival of  $0.75 \pm 0.07$ . They concluded that multi-drug therapy could be useful in augmenting survival in juvenile granulosa cell tumors, especially those of advanced stage. Thus, while all of the patients in our study had juvenile granulosa cell tumors

that have seemed to behave in a clinically benign fashion, this is not the universal experience.

Despite somewhat different findings between studies, all studies found a significant number of ovarian masses were malignant. Fortunately, ovarian malignancies in children are frequently found at an early stage and most respond favorably to chemotherapy. Skinner and Schlatter [11] reported survival in all patients with benign tumors and seven of ten patients with malignant lesions. Brown et al. [6] noted two deaths in patients in their study that included 18 malignancies. Both were in patients with endodermal sinus tumors. Despite epithelial cancers of advanced stage (two patients of stage III, both with positive second-look procedures), no patients with epithelial tumors had died at mean follow-up of 45.6 months ( $n = 4$ ). A review by Imai et al. [12] included 23 patients with malignancies, only three of whom died within 4 years of diagnosis.

As features and outcomes of pediatric ovarian tumors are more thoroughly studied, efforts are expanding to balance the need for effective treatment with conservation of ovarian function and fertility.

Though uncommon in children, the clinical spectrum of ovarian tumors ranges from largely benign mature teratomas to life-threatening, widely metastatic cancers. Using modern radiographic, surgical, and pathologic techniques available at pediatric referral centers, we found approximately half of ovarian tumors occurring in children are benign. Pain was the most common symptom, although presence of an abdominal mass was frequent, and other symptoms non-specific. Precocious puberty and/or increasing abdominal girth may be concurrent findings. Torsion was occasionally found at the time of diagnosis, more frequently with mature cystic teratomas than with malignant tumors. Almost all neoplasms presented as unilateral masses and rarely were metastatic at diagnosis. Almost half the patients presented at 7–12 years of age. The option of conservative surgical therapy depends on the stage of disease at the time of diagnosis. Most patients with malignancies clinically do well with few recurrent tumors. It is critical to consider the diagnosis of ovarian pathology including benign and malignant ovarian tumors in the differential diagnosis of even very young girls with abdominal and endocrine symptoms.

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