Journal of Pediatric Surgery 49 (2014) 144–148

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Predictors of ovarian malignancy in children: Overcoming clinical barriers of ovarian preservation

Jonathan C. Papic [a], S. Maria E. Finnell [a,b], James E. Slaven [c], Deborah F. Billmire [a], Frederick J. Rescorla [a,*], Charles M. Leys [a]

[a] Division of Pediatric Surgery, Department of Surgery, Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, IN, USA
[b] Children's Health Services Research, Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN, USA
[c] Department of Biostatistics, Indiana University, Indianapolis, IN, USA

ARTICLE INFO

Article history:
Received 22 September 2013
Accepted 30 September 2013

Key words:
Ovarian preservation
Fertility sparing
Ovarian mass
Ovarian malignancy
Children

ABSTRACT

Background/Purpose: Ovarian preservation is desirable in girls with benign ovarian masses. We aimed to 1) identify clinical predictors of malignant ovarian masses, 2) investigate how often ovarian tissue is present to preserve in benign masses, and 3) identify factors associated with successful ovarian preservation.
Methods: Retrospective analysis (1997–2012) of girls age 1–18 years with an ovarian mass managed operatively. Data on presenting symptoms, imaging, biochemical markers, treatment, outcome, and pathology were extracted.
Results: We identified 150 patients. Large mass size, solid components, and elevated tumor markers (AFP, βHCG, and/or LDH) were significantly predictive of malignancy. All masses <10 cm, predominantly cystic, and with negative tumor markers were benign. Masses with all three of these characteristics would decrease a 20% malignancy pretest probability to a posttest probability of 0.25%. Benign masses managed by oophorectomy contained normal ovarian tissue in 76% of the specimens. For benign masses, successful ovarian preservation was significantly associated with size <10 cm, predominantly cystic, laparoscopy, and absence of torsion or calcifications.
Conclusion: Ovarian masses that are <10 cm, primarily cystic, and have negative tumor markers are most likely benign. Viable ovarian tissue is frequently present in benign masses, so significant efforts should be made for ovarian preservation.

Ovarian masses are uncommon in children, with an estimated annual incidence of 2.6/100,000 [1]. The majority of these are benign neoplasms or nonneoplastic cysts [2–7]. Approximately 10–20% of ovarian masses are malignant, accounting for less than 1% of all pediatric cancers [8–10]. When a child presents with an ovarian mass, the preoperative work up should include efforts to differentiate a malignant from benign mass, as this affects the surgical approach, the type of procedure, and future reproductive health. For masses thought to be benign, ovarian preservation (cystectomy, partial oophorectomy) is recommended, as unnecessary removal of healthy ovarian tissue has documented negative effects [11–13].

In more recent years, preservation rates in girls with benign ovarian masses have increased from 15% in 1999 [14] to 39–61% [15–17], but is likely less than it could be [18]. In this study, we aimed to 1) identify clinical predictors to help discern malignant from benign ovarian masses, 2) investigate how often benign ovarian masses contain normal ovarian tissue that could be preserved, and 3) identify clinical characteristics associated with successful ovarian preservation in benign masses.

1. Methods

Girls age 1–18 years who underwent surgery for an ovarian mass by eight different pediatric surgeons at a single tertiary care children's hospital between January 1997 through June 2012 were retrospectively identified based on CPT and ICD-9 codes. Data on presenting symptoms, age, maximum diameter of mass, biochemical markers [including α-fetoprotein (AFP), beta human chorionic gonadotropin (βHCG) and lactate dehydrogenase (LDH)], procedure performed and technique, outcome, and pathology were extracted. Ovarian mass characteristics and size were determined by preoperative imaging, or by surgeon description and pathology reports if imaging not available. Infants less than 1 year of age, girls with a paratubal cyst, and those with ovarian torsion without an associated mass were excluded.

Univariate analysis consisted of Student's t-test for continuous variables and Chi-Square test for categorical variables. Because of low cell expected values, Fisher's Exact test was performed to validate Chi-Square tests. P values <0.05 were considered significant. Statistically significant clinical characteristics were analyzed with logistic

* Corresponding author. Division of Pediatric Surgery, Indiana University School of Medicine, Riley Hospital for Children, 702 Barnhill Drive – Suite 2500, Indianapolis IN 46202. Tel.: +1 317 274 5706; fax: +1 317 274 4491.
E-mail address: frescorl@iupui.edu (F.J. Rescorla).

0022-3468/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jpedsurg.2013.09.068

regression to test their association with malignancy and ovarian preservation. Factors associated with ovarian preservation were further tested in a multivariate regression model. Because of the low number of malignant tumors, multivariate regression was not performed on the predictors of malignancy. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

In a separate sub-analysis of our data, we also derived the posttest probability of a mass being malignant when negative for all statistically significant predictors of malignancy using similar methods to that described by Gorelick et al [19]. Sensitivity, specificity and negative likelihood ratios were calculated for each statistically significant predictor in our dataset. Predictor independence was confirmed by Fisher's Exact test and the predictors' negative likelihood ratios were multiplied for the combined negative likelihood ratio. An existing literature based pretest probability of any ovarian mass being malignant was converted to pretest odds. The combined negative likelihood ratio and pretest odds were multiplied yielding a posttest odds, which was then converted to posttest probability.

2. Results

Out of 150 patients identified, 132 (88%) patients had a benign mass and 18 (12%) patients had a malignant mass (Table 1). The mean age at time of surgery was 11.3 years (range 1–18 years, SD ± 4.0). Primary presenting symptoms included acute abdominal pain (n = 86, 57%), chronic abdominal pain—defined as duration ≥ 1 month (n = 17, 11%), palpable mass (n = 33, 22%), incidental finding during workup for unrelated medical condition (n = 12, 8%), precocious puberty (n = 1, 0.7%), and respiratory distress (n = 1, 0.7%). Principle pathology was in the right ovary in 75 patients (50%), left ovary 72 patients (48%), and 3 patients (2%) had bilateral disease.

Table 1
Clinical characteristics comparing malignant and benign ovarian masses found in 150 children.

	Malignant	Benign	P-value
No. of patients	18	132	
No. of procedures	19	133	
Age			
Age (y), mean ± SD	11.9 ± 3.7	11.2 ± 4.0	0.4868
Ages 1–8 y	3 (17%)	28 (21%)	0.8959
Ages 9–14 y	11 (61%)	78 (59%)	
Ages 15–18 y	4 (22%)	26 (20%)	
Symptoms			
Acute pain	10 (56%)	76 (58%)	0.1286
Chronic pain	1 (6%)	16 (12%)	
Palpable mass	5 (28%)	28 (21%)	
Incidental	1 (6%)	11 (8%)	
Precocious pub	0	1 (1%)	
Respiratory distress	1 (6%)	0	
Position			
Right	9 (50%)	66 (50%)	0.8087
Left	9 (40%)	63 (48%)	
Bilateral	0	3 (2%)	
Size			
Size (cm), mean ± SD	17.3 ± 14.0	10.9 ± 9.6	0.0009
≥10 cm	16 (89%)	60 (45%)	0.0005
<10 cm	2 (11%)	72 (55%)	
Characteristics			
Solid[a]	14 (78%)	49 (37%)	0.001
Cystic[b]	4 (22%)	83 (63%)	
Calcification	4 (22%)	48 (36%)	0.237
Torsion	1 (6%)	45 (34%)	0.0138
Tumor markers			
Pos marker	15/18 (83%)	2/92 (2%)	<0.0001
AFP	9/18 (50%)	0/90 (0%)	<0.0001
BHCG	6/18 (33%)	0/87 (0%)	<0.0001
LDH	9/13 (69%)	2/14 (14%)	0.0037

[a] Solid components identified.
[b] Includes simple and complex cyst.

Malignant ovarian masses were larger than benign masses (mean size 17.3 cm, range 7–30 cm vs 10.9 cm, range 2–40 cm) ($p < 0.05$) and more likely to have a solid component identified on imaging (78% vs 37%, $p < 0.05$) (Table 1). Torsion was present in only one patient with a malignant mass (6%) compared to 45 (34%) patients with a benign mass ($p < 0.05$). There was no statistically significant difference between groups in regard to mean age at time of surgery, presenting symptoms, and presence of calcifications on imaging.

When malignancy was analyzed by age group, (ages 1–8, 9–14, 15–18), the majority of malignant masses were identified in the 9–14 year old group (61%). However, the percentage of patients with a malignant mass within each age group remained constant, ages 1–8 (10%), 9–14 (12%) and 15–18 (13%) ($p = 0.90$), indicating that a child presenting with an ovarian mass has a similar risk of malignancy regardless of age. The tumor markers, AFP and βHCG were tested on 108 (72%) and 105 (70%) patients respectively, and LDH was tested on 27 (18%). At least one positive tumor marker (AFP, βHCG, or LDH) was present in 15/18 (83%) patients with malignant disease compared to 2/92 (2%) patients with a benign mass. LDH alone was elevated in two patients with benign tumors.

2.1. Predictors of malignancy

In the univariate analysis, clinical characteristics significantly associated with malignancy include, size ≥10 cm OR 9.60 (2.12, 43.42), presence of solid components OR 5.93 (1.85, 19.03) and a positive tumor marker (AFP, βHCG, or LDH) OR 225 (34.65, >999) (Table 2). Thirty ovarian masses were negative for all three predictors (size <10 cm, no solid components, and no positive markers) and all 30 were benign, though 17 (57%) of these were treated with an oophorectomy.

In our sub-analysis to derive the posttest probability of a mass being malignant when negative for all three predictors (size <10 cm, no solid components, and no positive markers) we calculated a combined negative likelihood ratio of 0.01 ($0.2 \times 0.35 \times 0.17$). Given the conservative pretest probability of any ovarian mass being malignant of 20% (3), the calculated posttest probability is 0.25%. That means that, based on our data, an ovarian mass <10 cm, with no solid components, and no positive markers has only a 0.25% probability of being malignant.

2.2. Pathology review

Pathology reports were reviewed and categorized by diagnosis (Table 3). Additionally, pathology reports of benign masses treated with oophorectomy were reviewed to determine if residual normal ovarian tissue was present in the specimen. Reports for 72 of the 100 (72%) benign oophorectomy specimens had a specific comment by the pathologist regarding the presence or absence of identifiable ovarian tissue. Normal ovarian tissue was identified in 55/72 (76%) specimens (18 identified grossly, 37 microscopically). Necrotic ovarian tissue was identified in 8/72 (11%) specimens, and no identifiable gross or microscopic ovarian tissue occurred in only 9/72 (13%) (Table 4).

Table 2
Odds ratios of clinical characteristics for malignancy.

	Malignant n = 18	Benign n = 132	Univariate OR (95% CI)
Size ≥ 10 cm	16 (88%)	60 (45%)	9.60 (2.12, 43.42)
Solid component	14 (78%)	49 (37%)	5.93 (1.85, 19.03)
Positive marker[a]	12/18 (67%)	0/92 (0%)	225.00 (34.65, >999)
Calcification	4 (21%)	48 (36%)	0.50 (0.16, 1.61)

[a] AFP, βHCG, and/or LDH.