Original Study

A Preoperative Scoring System for Adnexal Mass in Children and Adolescents to Preserve Their Future Fertility

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A B S T R A C T

Study Objective: To develop a predictive score for ovarian malignancy to avoid unnecessary adnexectomy in cases of adnexal mass in pediatric and adolescent girls.
Design: A population-based retrospective study on girls who underwent surgery for an ovarian mass with normal levels of human chorionic gonadotrophin and alpha fetoprotein between 1996 and 2016.
Setting: Rennes University Hospital, Rennes, France.
Participants: Eighty-one patients who received surgery for ovarian tumor.
Main Outcome Measures: The main outcome measure was the rate of malignant and borderline tumor. A preoperative scoring system was constructed after multivariate analysis.
Results: The rate of malignant ovarian tumor was 6/81 (7%), borderline tumor was 7/81 (9%) (ie, outcome measure: 16%), and benign tumor was 84%. In a univariate analysis, the characteristics significantly associated with malignancy were early puberty, palpable mass, size and content of the tumor, and positive epithelial tumor markers (carcinoma antigen 125, carcinoembryonic antigen, and carcinoma antigen 19-9). The predictive malignancy score was on the basis of 2 variables obtained after multivariate analysis: tumor size and cystic content. The score defined 3 groups at risk for malignancy: low risk, middle-risk, and high-risk. The sensitivity for detecting malignancy was 1.3% (95% confidence interval [CI], 0.1-18.4), 26.2% (95% CI, 11.6-49.0), and 53.1% (95% CI, 29.1-75.8), respectively.
Conclusion: We set up a simple predictive score of malignancy on the basis of objective criteria to help decision-making on whether or not ovarian-sparing surgery is feasible in case of children and adolescents with ovarian tumors and normal human chorionic gonadotrophin and alpha fetoprotein levels while ensuring oncologic safety.
Key Words: Adnexal mass, Children, Adolescent, Surgery, Ovarian malignancy, Score, Ovarian preservation

Introduction

Ovarian tumors in children and adolescents are rare, with an estimated incidence in girls of 2.2/100,000.[1−3] Most ovarian tumors in this population are benign and often organic; only 10%-20% are malignant.[4,5] Among children and adolescents, only 1% of pediatric cancers are malignant tumors of the ovary.[4−9] The age of the child does not change the risk of malignant ovarian tumors. Germ-cell tumors represent most ovarian tumors and include mature benign teratomas (dermoid cysts).[10] Overall, patients with malignant germ-cell tumors have a good prognosis.[11] Sex-cord stromal tumors are regularly seen in pediatrics. The prognosis of these tumors is related to the initial surgery, which must be complete.[12]

The discovery of an ovarian mass in a child presents a dilemma regarding the optimal treatment. An immediate oophorectomy, or adnexectomy, has the best oncological safety, whereas an ovarian cystectomy better preserves the patient's fertility. Indeed, an ovariectomy or adnexectomy in childhood is correlated with a lower spontaneous pregnancy rate (45.5%)[13,14] and premature ovarian failure,[15] which is an ongoing concern. Of note, in Western countries, because of societal evolution, pregnancy occurs later, with 22% of births occurring in women older than 35 years of age.[16] Thus, women who underwent ovariectomy in childhood are particularly vulnerable to ovarian failure at the time of conception, and ovarian preservation in children is crucial to protect their future fertility. However, oncologic surgery remains mandatory for the treatment of ovarian cancer to avoid compromising an otherwise good prognosis. Indeed, the main risk of ovarian-sparing surgery in case of malignant germ-cell tumor is either spillage or recurrence on the preserved parenchyma.[10,17]

The rates of conservative surgery for ovarian mass in pediatric patients are 18%-72%[1,18−20] depending on surgeon habits and cohort studies, reflecting the fact that most benign adnexal masses in children are removed via

oophorectomy. Preoperative analysis of the lesion remains crucial for tailoring surgical management (ie, appropriately choosing between oophorectomy and ovarian conservative management).[21] Although International Ovarian Tumor Analysis (IOTA) classification for adnexal masses is available for adult women,[22] there are no objective criteria or reproducible tools to preoperatively predict the risk of malignancy in children with an adnexal mass.

The aim of this study was to determine the predictive factors of malignancy in pediatric patients with an adnexal mass and to develop a simple score for predicting malignancy.

Materials and Methods

Objective and Design of the Study

This was a population-based retrospective study conducted from January 1996 to April 2016 in a tertiary hospital (Rennes Teaching Hospital, France). Inclusion criteria were patients aged 0-18 years with a diagnosis of ovarian mass who underwent surgical treatment. Exclusion criteria were positive germinal tumor markers: alpha fetoprotein (αFP) greater than 10 ng/mL, human chorionic gonadotropin (HCG) greater than 5 mU/mL, or a functional follicle on sonography or pathological analysis. Indeed, positive germinal tumor markers are always associated with a malignant germ-cell tumor.[4,11,23,24] We differentiated germinal tumor markers (αFP and HCG) from epithelial tumor markers (carcinoma antigen [CA]-125, carcinoembryonic antigen, and CA 19-9).

The main outcome measure was defined as the finding of ovarian cancer or a borderline ovarian tumor on the final pathological analysis because these findings usually required adnexectomy. Ovarian borderline lesions were diagnosed upon pathological analysis according to the 2014 World Health Organization criteria,[25] as was ovarian cancer. All final pathological analyses were reviewed by a certified pathologist (S.H.).

This study was approved by the local institutional review board (CEROG 2016-GYN-1003).

Data Collection

The medical database from the pediatric surgery department was used to select the patients. The data were collected from the patients' medical records, which were stored in the hospital's archiving system. Data regarding the patient's age at diagnosis, hormonal status (puberty, defined by the presence of a menstrual cycle), medical history, and clinical symptoms were collected. According to the symptoms, a palpable mass was defined as the palpation of a mass by the patient or her physician, or as an increase in the abdominal perimeter observed by the patient.

The characteristics of the ovarian lesions were obtained from preoperative imaging (ultrasound, abdominopelvic computed tomography imaging and/or pelvic magnetic resonance imaging [MRI]) and described according to the IOTA classification[22] for pelvic ultrasound using the following 10 criteria: maximum diameter of the mass, the presence of a septum, the regularity of the wall, type of cyst (multilocular, solid multilocular, unilocular, solid unilocular, solid), cyst content, solid papillary projection, posterior shadow cone, Doppler signal strength, and the presence of ascites or a peritoneal implant. All preoperative imaging scans were reviewed by a certified specialist in the imaging of the female reproductive system who was blind to the final pathological analysis.

Data regarding elevated levels of tumor markers (αFP > 10 ng/mL, HCG > 5 mU/mL, carcinoembryonic antigen > 30 μg/L, cancer antigen CA-125 > 35 U/mL, and CA 19-9 > 37 U/mL), the type of surgery performed, association with an adnexal torsion, complications of the surgical procedure, and pathological findings were also collected.

The lesions were classified as benign and nonbenign comprising borderline and malignant tumors.

Statistical Analyses

For quantitative variables, data were expressed as mean ± SD if normally distributed and median (range) if not normally distributed. For qualitative variables, data were expressed as n (%). Comparisons between groups were performed using t tests for normally distributed variables, Wilcoxon for non-normally distributed variables, and χ^2 test or Fisher exact test for categorical variables. A forward logistic regression analysis was applied to the statistically significant variables to test their association with malignancy. All variables for which statistical significance was less than 0.2 were introduced into models. Optimal cutoff values were obtained using optimization of the Youden index from area under the receiver operating curve (ROC) analysis. The predictive malignancy score was constructed from variables derived from the multivariate analysis. Sensitivity, specificity, negative predictive value, and positive predictive value were also calculated. A P value of less than .05 was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc).

Results

An adnexal mass was detected in 89 children during the study period. One patient was excluded because of follicle diagnosis, and 7 others were excluded because of high levels of serum αFP and HCG, which are known positive markers of germinal tumor (Fig. 1). All 7 of these patients underwent ovariectomy surgery and final ovarian germinal tumor diagnosis. Finally, 81 patients were included in the study.

Descriptive Data

The characteristics of the patients are summarized in Table 1. The mean (±SD) age of the population was 13.1 (±4.7) years, without significant difference between the 2 groups ($P = .40$). There were 36 (44%) right ovarian masses and 45 (56%) left ovarian masses. There were 4 (31%)
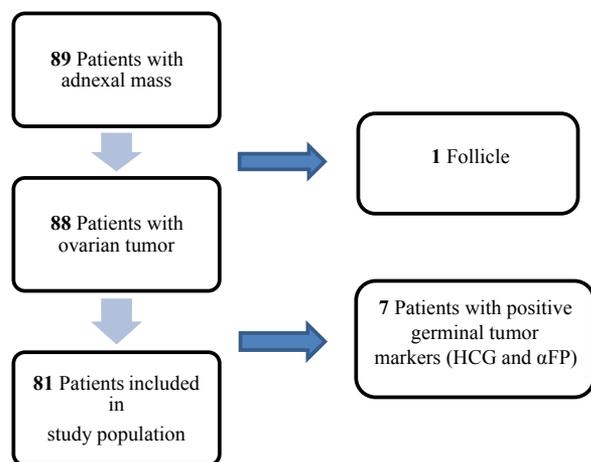
Fig. 1. Flow chart. αFP, alpha fetoprotein; HCG, human chorionic gonadotrophin.

malignant tumors and 26 (38%) benign tumors among the prepubescent patients (*P* = .76).

Laparotomy was performed in 20 patients (25%), and 61 (75%) underwent laparoscopic surgery, including 22 conversions to laparotomy. Among these 22 patients with conversions, 1 tumor was borderline, and 21 were benign (7 adnexal masses had a size > 100 mm). Finally, 42 laparotomies (52%) were performed (32 horizontal and 10 median laparotomies) for 30 benign tumors (44.1%), and 12 malignant tumors (92.3%; *P* < .0001).

Of note, there were 14 adnexal torsions, all due to a benign mass. Ten underwent a nonconservative treatment and 4 either tumorectomy or isolated adnexal detorsion.

The pathological results are presented in Table 2. Briefly, 7 patients had an epithelial borderline ovarian tumor and 6 had ovarian cancer (5 nonepithelial tumors and 1 epithelial tumor). Thus, 13/81 (16%) of the patients had an adnexal tumor that required oncologic surgical treatment (ie, nonconservative treatment [primary outcome measure]).

In the present study, all patients with malignant tumors were treated with nonconservative surgery (oophorectomy or adnexectomy), and 3 of the 7 patients with borderline tumors underwent cystectomy.

Data Analyses

Symptoms were significantly associated with malignancy (*P* = .01), especially early puberty and palpable mass (Table 1).

Preoperative ultrasound imaging was performed for 79 patients; 24 patients underwent computed tomography imaging, and 22 underwent MRI. The size of the lesion was significantly associated with malignancy (*P* < .0003) and all malignant lesions exceeded 65 mm in diameter with a

Table 1
Preoperative Patient Characteristics

	Study Population (N = 81)	Malignant Tumor (n = 13; 16%)	Benign Tumor (n = 68; 84%)	*P*
Age, years				
Mean ± SD	13.1 ± 4.7	13.8 ± 5 .2	13 ± 4.6	
Median (range)	15 (0-19)	15 (3-18)	15 (0-19)	.40
0-8	15 (19%)	2 (15%)	13 (19%)	.68
9-13	14 (17%)	1 (8%)	13 (19%)	
Older than 13	52 (64%)	10 (77%)	42 (62%)	
Prepubescent hormonal status	30 (37%)	4 (31%)	26 (38%)	.76
BMI, mean ± SD	21.7 ± 3.6	20.6 ± 3.0	22.0 ± 3.7	.41
Symptoms				.01
Palpable mass	13 (16%)	4 (31%)	9 (13%)	
Acute pain	49 (60%)	6 (46%)	43 (63%)	
Other	17 (21%)	1 (8%)	16 (24%)	
Early puberty	2 (2%)	2 (15%)	0	
Sonography size, mm				
Mean ± SD	99.1 ± 70.9	166.1 ± 70.3	86.3 ± 63.9	
Median (range)	70 (19-360)	170 (65-260)	66 (19-360)	.0003
Larger than 100	30 (37%)	10 (77%)	20 (29%)	.003
Type of ovarian mass				.0002
Multilocular	7 (9%)	2 (15%)	5 (7%)	
Solid multilocular	10 (12%)	5 (38%)	5 (7%)	
Unilocular	36 (44%)	3 (23%)	33 (49%)	
Solid unilocular	27 (33%)	2 (15%)	25 (37%)	
Solid	1 (1%)	1 (8%)	0	
Sonography characteristic				
Solid	38 (47%)	8 (62%)	30 (44%)	.25
SPP	37 (50%)	4 (44%)	33 (51%)	1.00
Calcification	20 (25%)	2 (15%)	18 (27%)	.79
Cystic	29 (40%)	3 (23%)	26 (44%)	.16
Ascites	4 (5%)	2 (15%)	2 (3%)	.16
Peritoneal implant	1 (1%)	1 (8%)	0	.17
Tumor markers				
Positive marker	16 (24%)	7 (54%)	9 (17%)	.009
CA-125	13 (16%)	6 (46%)	7 (10%)	.005
CA 19-9	7 (9%)	3 (23%)	4 (6%)	.038
CEA	2 (3%)	2 (15%)	0	.027
Torsion	14 (17%)	0	14 (21%)	.11

Bold values represents the *P* value <0.05.
CEA, carcinoembryonic antigen; BMI, body mass index; CA, carcinoma antigen; SPP, solid papillary projection.

Table 2
Pathologic Findings of Pediatric Ovarian Masses

Finding	Patients, n	%
Benign	68	84
Germ-cell tumor	42	–
Mature teratoma	42	–
Epithelial	24	–
Serous cystadenoma	16	–
Mucinous cystadenoma	8	–
Sex-cord stromal tumor	1	–
Sclerosing tumor	1	–
Indeterminate tumor	2	–
Borderline	7	9
Serous	3	–
Mucinous	4	–
Malignant	6	7
Germ-cell tumor	2	–
Dysgerminoma	1	–
Immature teratoma	1	–
Epithelial	1	–
Mucinous cystadenocarcinoma	1	–
Sex-cord stromal tumor	2	–
Juvenile granulosa tumor	2	–
Secondary	1	–

Table 4
Score Predictive of Malignancy

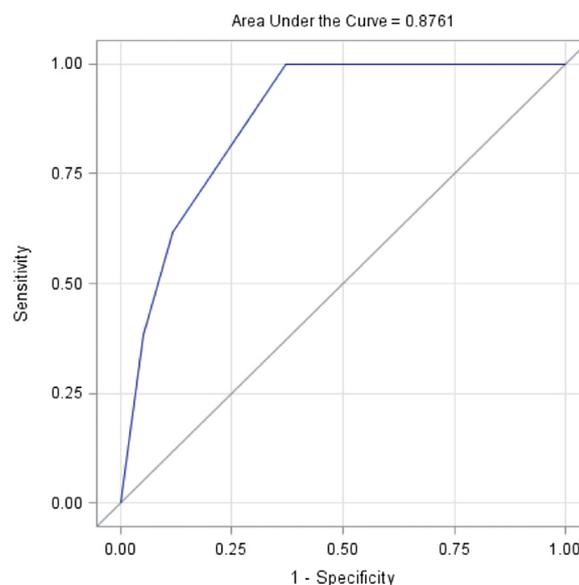| Variable	Score	Predictive Risk (95% CI)
Size of lesion, mm		
Less than 65	0	–
65-130	25	–
Greater than 130	41	–
Unilocular cystic tumor		
Yes	0	–
No	9	–
Total score		
Low-risk group	0-25	1.3% (0.1-18.4)
Middle-risk group	26-40	26.2% (11.6-49)
High-risk group	Greater than 40	53.1% (29.1-75.8)

CI, confidence interval.

multivariate analysis. A ROC was plotted to determine the sensitivity and specificity of the score (Fig. 2). The area under the curve of the ROC was 0.88 (0.80-0.95).

Following the IOTA recommendations with a single cutoff at 100 mm, the multivariate odds ratio was 7.68 (1.96-30.07). To maximize the statistical significance of the "lesion size" variable we selected 2 cutoffs: 65 mm and 130 mm. The choice of 2 cutoff points to define a population at low risk (<65 mm) and a population at high risk (>130 mm) provided a clinical prediction rule with a good diagnostic performance: the low risk cutoff point defined a model with a sensitivity of 100% and the high risk cutoff point defined a model with a specificity of 88%.

The score was constructed from the logistic model coefficients (Table 4). Using a score cutoff of greater than 25, the sensitivity, specificity, positive predictive value, and negative predictive value for predicting malignancy were 100%, 63%, 37%, and 100%, respectively.

mean size of 166.1 mm (70.3) vs 86.3 mm (63.9) for benign lesions in the univariate analysis. A lesion size greater than 100 mm according to the IOTA classification cutoff was correlated with ovarian cancer (P = .003) as determined in a univariate analysis (Table 1).

Among the morphological criteria used in echography to characterize a malignant tumor, the type of ovarian mass was significantly associated with malignancy (P = .002). In this study, a solid multilocular mass was identified in 5/13 (38%) patients with malignant tumors vs 5/68 (7%) patients with benign tumors (Table 1).

Tumor markers were significantly associated with ovarian malignancy (P = .009) and were measured in 64/81 (79%) patients. Tumor markers were elevated in 7/13 (54%) patients with malignant tumors vs 9/51 (17%) patients with benign tumors.

On the basis of 72 patients who underwent preoperative sonography, the multivariate analysis defined 2 predictive factors of malignancy and borderline tumor: the size of the tumor (<65 mm, 65-130 mm, and > 130 mm) and the ultrasound aspect of the tumor (unilocular cystic tumor or not; Table 3).

Malignancy Scoring System

A predictive score for malignancy (Table 4) was constructed using the 2 variables associated with malignant ovarian tumor or borderline tumor derived from the

Clinical Utility of the Score

The score allowed stratification of the population in 3 groups as low risk, middle risk, and high risk of malignancy.

Table 3
Predictive Factors of Malignancy and Borderline Tumors in Multivariate Analysis (N = 72)

Factor	Malignant and Borderline (n = 13)	Benign (n = 59)	Multivariate OR (95% CI)
Size less than 65 mm	0	27 (46%)	1
Size 65-130 mm	5 (38%)	25 (42%)	10.89 (0.57-210.0)
Size greater than 130 mm	8 (62%)	7 (12%)	74.54 (3.58-999.99)
Unilocular cystic tumor	3 (23%)	26 (44%)	1
Other type of tumor	10 (77%)	33 (56%)	3.63 (0.74-17.84)

CI, confidence interval; OR, odds ratio.

Fig. 2. Receiver operating curve of the score to predict malignancy.

This was applied to our study population following the rules that low risk was due to ovarian-sparing surgery, high risk to nonsparing surgery, and middle risk to further investigations or discussion. This resulted in 46 (57%) patients who should be spared adnexectomies, 16 (20%) patients who would have been referred for nonconservative treatment, and 19 (23%) who would have required more investigations and discussion on the risk and benefits of each option. This led to 80% of nonradical first-line treatment (conservative treatment or implement investigations).

Discussion

In the present study, we created a simple score for predicting malignancy in children and adolescents with adnexal mass and therefore helped to determine whether conservative or radical surgery was the optimal treatment strategy. We built a scoring system using factors found in the multivariate analysis: tumor size and cyst component. This tool provides ensured oncologic safety while preserving fertility. In our series, fertility would be directly spared in 57% of children with adnexal mass, and 23% of the patients would require more investigations before making the decision on ovarian-sparing surgery. All patients with ovarian cancer (borderline or invasive) would undergo either nonconservative surgical treatment or continuation of the workup, which is, at present day, the correct oncologic decision.

Some weaknesses of the present study must be mentioned, particularly in relation to the misinterpretation of data, classification bias, or missing data, because of the study's retrospective nature. Nevertheless, our results are similar to those previously reported in populations ranking from 41 to 112 patients with a malignancy prevalence of 10%-20%. This prevalence might vary depending on the age at screening and the availability of tertiary screening centers. Conservative surgery ratios vary between 15% and 87% according to recent studies.[1,18—20,26]

Many studies have sought to identify predictive characteristics to guide the decision of conservative vs radical surgery.[17,27—30] The detection of αFP and HCG (marker of germinal tumor) in blood testing strongly indicated that the tumor was malignant, which is why patients with positive germinal markers were excluded from our study because they required nonconservative surgical treatment for oncologic purposes. To predict whether a tumor might be benign or malignant, its characteristics are determined using pelvic echography or MRI. For example, tumors greater than 7.5-8 cm are at high risk of being malignant, according to published data.[19,26,27,31] The threshold varies depending on the studies and specificity and sensitivity levels chosen: in the present study, a tumor size that correlated with malignancy was 65 mm or larger (as much as 100 mm or more). As opposed to adult women, there is no classification dedicated to the pediatric population to differentiate benign from malignant tumors on the basis of their ultrasound features (or MRI features). Thus, in the present study, we used the IOTA classification to sort and interpret preoperative sonography pictures.[22,32] Using the simple rules proposed in the IOTA classification, our study showed first that

solid multilocular ovarian mass is significantly associated with malignancy in children.

The Ueland Index, described by Stankovic, is an ultrasonographic algorithm tool specific to the pediatric population.[33,34] Its 2 criteria are the volume and structural characteristics of the tumor. A tumor is considered benign if it is less than 5 cm and malignant if greater than 7 cm in diameter. This tool predicted the risk of malignancy with a sensitivity of 90% and a specificity of 94%. In another recent study, Stankovic showed that discrimination between benign and malignant tumors in pediatric and adolescent patients was greater with the Ueland index than with the search for the ovarian crescent sign. Indeed, there is a lack of reproducibility in the ultrasonographic search for the ovarian crescent sign,[35] because it is difficult to spot when the mass is greater than 5 cm in abdominal echography; therefore, it is unreliable as a discriminating sign. Nevertheless, the Ueland Index had some weakness because it was determined as an algorithm and not on the basis of a statistical tool, such as logistic regression, as our proposed robust score. Our score and the Stankovic algorithm still require external validation using a multicenter prospective cohort.

Despite that previous studies have shown that size and complexity were important predictors of malignancy,[19,20,26,36,37] none of the different scoring system or preoperative stratification has proven its clear utility. For example, following the recommendations published by Rogers et al,[20] 15 patients in our series would have had malignant tumor management because of the size of their ovarian masses greater than 8 cm. We also applied the preoperative risk stratification described by Madenci et al in 2016 on our series.[36] This led to 54.5% who would be treated with ovarian-sparing surgery, 10% nonsparing surgery, and 35.5% of doubtful cases. Our score led to 57%, 20%, and 23%, respectively. In their series, Madenci et al[36] reported fewer malignant tumors (8% vs 16%) and included functional cyst (23%) that we did not consider as ovarian tumors and were excluded in our study. As stated in many studies, every case should be unique and discussed between family and surgeons. Thus, we propose a simple score to add an objective value to the discussion and decision-making and improve the armamentarium that helps dealing with ovarian tumors. Using this score in a daily manner would be easier and less tedious than following most of the risk stratifications previously described. In practice, when seeing children with adnexal mass, physicians should perform an ultrasound scan and the usual workup with tumor markers. In case of confirmed ovarian tumor with negative αFP and HCG, one could apply this scoring system and adapt the strategy and the speech given to the family following the predictive risk described in Table 4. Patients in the low-risk group could undergo ovarian-sparing surgery, when possible after MRI to guide the surgery. In the middle-risk group, a complementary workup of at least an MRI scan should be mandatory, taking into account the 26% predictive risk of malignancy. Patients belonging to the high-risk group should be proposed a nonconservative treatment.

In our study, 10 of 14 adnexal torsions were treated with oophorectomy or adnexectomy. Since the introduction of the national or international recommendations in the

gynecologic society,[38,39] this treatment strategy has to change. The revised approach is on the basis of the recognition that even if the ovary has an infarcted appearance, it might recover normal endocrine function[13]; thus, conservative treatment should be attempted in all cases.[40–42] Indeed, in our study, adnexal torsion was never associated with a malignant or borderline tumor, as confirmed by published data.[13,40]

In the literature, the specialty of the surgeon was shown to influence the decision for ovarian preservation[31,43] with more conservative treatments performed by gynecologic surgeons and less conservative treatment performed by pediatric surgeons. This difference in care outcome should be addressed. By using the score evaluated in this study, the probability of malignancy can be better evaluated preoperatively, allowing a better-informed decision regarding ovarian preservation. Our score allowed 57% of ovarian conservative surgeries and 23% of patients requiring more investigations. The ovarian-sparing surgery rate must be improved in the future and we need to work with radiologist to improve the care of the 23% of doubtful cases. It is likely that adnexal mass in children should be explored systematically using MRI combined with perfusion- and diffusion-weighted MRI as used in adult women with ovarian mass.[44] These new tools must be validated in children to improve the ovarian conservation rate in case of adnexal mass because these approaches have only been recently described.[45,46] It could also help to visualize healthy ovarian tissue remnants in case of large tumors.

Conclusion

To our knowledge, this is the first published simple scoring system for predicting malignancy in children and adolescents with an adnexal mass. It is on the basis of easily obtained sonographic data (size and echogenicity of the tumor) and can be applied in children with an adnexal mass and normal germinal tumor marker levels. The score could be used to guide decision-making regarding conservative vs nonconservative ovarian surgical treatment and might therefore increase the rate of fertility preservation while ensuring good oncologic safety in a larger number of patients. In our study, 80% of the children with an adnexal mass might undergo ovarian-sparing surgery (57% of first-line conservative treatment and 23% requiring more investigations before decision) on the basis of reproducible criteria. However, this scoring system still requires external validation in a prospective multicenter study before it can be routinely used in a clinical setting. MRI combined with perfusion- and diffusion-weighted MRI applied to the pediatric population could be the next step in improving the rate of ovarian preservation surgery in children with adnexal mass. Of note, conservative management in cases of adnexal torsion in children, as in adults, will also help to increase the rate of ovarian-sparing surgery.

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