Ovary-sparing surgery for benign pediatric ovarian masses

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Purpose of review
This review highlights progress in the management of pediatric ovarian neoplasms. Recent research has identified disparities in the management of patients with benign ovarian neoplasms based on a variety of factors. However, the long-term effects of unilateral oophorectomy have prompted an emphasis on ovary-sparing surgery (OSS) for benign masses. One of the challenges still facing providers is the preoperative differentiation between benign and malignant masses.

Recent findings
Recent studies highlight the variability in practice patterns surrounding the management of benign ovarian neoplasms. Progress continues to be made in identifying reliable factors that can be used to inform preoperative risk stratification of patients who present with ovarian neoplasms. These factors include imaging characteristics, symptoms and tumor markers. In addition, the safety of OSS with regard to recurrence and upstaging in appropriate settings continues to be demonstrated.

Summary
This review highlights the importance of multidisciplinary collaboration in the treatment of ovarian neoplasms given the varied surgical approach by specialty. Multiple retrospective studies have identified factors that can be used for preoperative risk stratification and selection of patients for OSS. Prospective studies evaluating the accuracy of these factors for preoperative risk stratification are needed.

Keywords
benign ovarian neoplasms, ovary-sparing surgery, preoperative risk stratification

INTRODUCTION

Ovarian lesions in the pediatric population are relatively rare. The differential diagnosis of ovarian lesions depends on the patient presentation and may include benign or malignant neoplasms, cysts, tubo-ovarian abscesses, congenital anomalies or ectopic pregnancies. Although the majority of these diseases may be readily distinguished on imaging, one of the more challenging distinctions is determining whether an ovarian neoplasm is benign or malignant. Benign neoplasms common among pediatric patients include mature teratomas, serous cystadenomas and mucinous cystadenomas. Common malignant tumors in pediatric patients include immature teratomas and sex cord stromal tumors [1].

The evaluation of patients with an ovarian mass includes history, physical examination, laboratory tests and imaging findings. Prior to determining their final disease, ovarian neoplasms can be classified into cystic, complex or solid based on imaging findings [2]. If surgical treatment is warranted, patients may be cared for by providers of different specialties including pediatric surgeons, pediatric and adolescent gynecologists (PAGs) or adult gynecologists. On the basis of preoperative findings, a surgeon may decide to proceed with ovary-sparing surgery (OSS) or removal of the entire ovary (oophorectomy).

Promotion of OSS for benign masses is important because oophorectomy has been associated with negative long-term consequences. Potential negative effects of oophorectomy include an increased risk for early menopause and premature ovarian failure, which are associated with impaired

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KEY POINTS

- Recent research has shown that pediatric surgeons and PAGs treat benign ovarian disease differently, with pediatric surgeons being more likely to perform oophorectomies.
- Preoperative risk factors, such as tumor markers, physical examination, history and imaging findings, can be used to perform preoperative risk stratification and guide operative decision making.
- Education and collaboration between specialties using preoperative risk stratification to evaluate high-risk patients can help decrease rates of oophorectomy for benign disease.

sexual health, low bone density, neurologic disease and heart disease in adulthood [3,4]; and a shorter reproductive lifespan and poorer response to ovarian stimulation for assisted reproduction [5,6▪]. Increased awareness of these potential negative effects of oophorectomy has led to changes in the management of benign ovarian lesions in children. This review highlights factors that have recently been identified as influencing the surgical procedure performed for pediatric ovarian masses.

VARIABILITY IN THE MANAGEMENT OF OVARIAN LESIONS

In contrast to adults, the majority of ovarian neoplasms in children are benign. Previous studies have found that malignancy occurs in approximately 10–20% of neoplasms identified in children [7,8▪▪,9]. Depending on the healthcare resources available, a child who presents with an ovarian mass may be operated on by pediatric surgeons, PAGs or adult gynecologists and may undergo an oophorectomy or OSS. OSS is considered the standard surgical approach for benign lesions in adults and entails removal of the tumor only, leaving the surrounding normal ovary in place. Although the most common types of ovarian lesions in adults differ from those in children, recent research has shown that there is no standard surgical approach to benign ovarian masses among pediatric practitioners [10].

In a 2017 study by Gonzalez *et al.* [11], the authors analyzed the Pediatric Health Information System (PHIS) to identify patients 6–21 years of age with a benign ovarian lesion who underwent ovarian surgery from 2006 to 2014. They subsequently identified various patient-level and hospital-level factors associated with patients undergoing an oophorectomy for a benign mass. Overall, 44.5% of patients with a benign ovarian neoplasm underwent an oophorectomy with the rates of OSS varying significantly across hospitals from 22 to 77%. They also identified that pediatric surgeons were less likely than PAGs to perform OSS for benign disease [odds ratio (OR) 0.27, 95% confidence interval (CI): 0.17–0.43, $P < .001$]. Other patient-level characteristics associated with lower odds of OSS being performed for benign disease included younger age (OR 0.94, 95% CI: 0.90–0.98, P 0.007), and patients who were admitted through the emergency department (OR 0.76, 95% CI: 0.58–0.99, $P = 0.04$). The finding that gynecologists were more likely than pediatric surgeons to perform OSS was also found in a retrospective, single-institution study by Bergeron *et al.* [12]. They adjusted for confounding factors such as age, BMI, ovary mass size and urgency of surgery across 194 cases, and found that gynecologists were significantly more likely than surgeons to perform OSS for benign adnexal masses (OR 1.84, 95% CI: 0.88–3.84).

Another 2017 database study by Kapp *et al.* [13] performed a similar analysis utilizing the National Inpatient Sample examining girls less than 18 years of age who underwent surgery for a cyst or benign ovarian neoplasm from 2005 to 2011. They found that overall 36% of patients had an oophorectomy for benign disease or a cystic lesion, and on multivariate analysis, oophorectomy was associated with younger age (OR 1.45, 95% CI: 1.26–1.68) and open surgical approach as compared to laparoscopy (OR 2.3, 95% CI: 1.99–2.68). They also identified that patients who were treated in the Midwest or South had higher rates of oophorectomy (OR 2.04, 95% CI: 1.53–1.73, and OR 1.99, 95% CI 1.52–2.59, respectively) and patients with a high socioeconomic status were less likely to undergo an oophorectomy when compared to patients from a low socioeconomic status (OR 0.76, 95% CI: 0.59–0.98).

The variability in management of patients with benign ovarian lesions appears to be based on a variety of factors including hospital and surgeon specialty. On the basis of this variability, our institution recently performed a quality improvement initiative using multidisciplinary education and collaboration to improve the rate of OSS for benign neoplasms [14▪]. The initial OSS rate for benign disease prior to the beginning of the quality improvement project was 29% from 2012 to 2016. After the initiation of a multidisciplinary treatment team with the utilization of a treatment algorithm, the group was able to increase the OSS rate to 96% for benign lesions over the course of 1 year. The success of this quality improvement initiative was based on education, multidisciplinary collaboration and a standardized algorithm to preoperatively identify lesions with a high likelihood of being benign. Preoperative risk stratification of pediatric

Table 1. Factors associated with a higher likelihood of malignancy

Patient characteristics/ symptoms	Younger age
	Precocious puberty
	Virilization
	Abdominal bloating
	History of ovarian malignancy
Elevated tumor markers	α-Fetoprotein (AFP)
	Lactate dehydrogenase (LDH)
	β Human chorionic gonadotropin (β HCG)
	Cancer antigen 125 (CA 125)
	Cancer antigen 19-9 (CA 19-9)
	Inhibin A
	Inhibin B
Imaging characteristics	Solid components
	Papillary projections
	Ill-defined borders
	Thick septations
	Extension into adjacent structures
	Ascites
	Lymphadenopathy
	Metastatic disease

ovarian masses is critical to promoting OSS for benign ovarian masses and remains an important area of ongoing research.

PREOPERATIVE RISK STRATIFICATION

The critical step to increasing rates of OSS for benign masses is accurate preoperative risk stratification that can discriminate between benign and malignant ovarian disease. Patient history and physical examination, imaging studies and tumor markers may aid with preoperative risk stratification. Although no widely accepted guidelines exist, several studies report factors that can be used to differentiate between benign and malignant ovarian disease (Table 1) [1,15–17].

Imaging studies can provide useful information for risk stratification based on the size and appearance of an ovarian neoplasm. In one report of 424 pediatric patients, tumors 8 cm or larger on preoperative imaging were associated with 19 times higher odds of malignancy as compared to smaller tumors with no malignancies identified in masses smaller than 6 cm [15]. However, size alone should not be an indication for oophorectomy because larger ovarian lesions are still most likely to be benign in the absence of worrisome ultrasound findings or elevated tumor markers. Worrisome imaging characteristics that should raise the suspicion for malignancy include a large solid component, thick septations and ascites [1]. In a series of 126 patients reported by Rogers *et al.* [17], all of the malignant tumors had complex features on ultrasound. Another series of 18 patients by Emil *et al.* [18] confirmed the ability of MRI to differentiate between functional versus neoplastic lesions with a sensitivity of 89%, specificity of 94%, negative predictive value of 94%, positive predictive value of 89% and accuracy of 93%.

Tumor markers can also serve as useful adjuncts in preoperative risk stratification. In a study by Depoers *et al.* [7], they found that the tumor markers CA-125 and CA 19–9 were elevated in 54% (7/13) of patients with malignant disease as compared to only 17% (9/51) of patients with benign disease. However, their study excluded patients with positive germ cell tumor markers [α-fetoprotein (AFP) and β-human chorionic gonadotropin (β-HCG)], based on their conclusion that 'positive germinal tumor markers are always associated with a malignant germ-cell tumor.' In a study by Oltmann *et al.* [15], tumor markers were elevated in 51% of malignancies, but only 6.5% of benign cases. One review recommends sending tumor markers when imaging reveals high-risk features [1]. As pediatric patients may present with various malignant diseases including epithelial and germ-cell tumors, we recommend testing of markers associated with various tumor lines, including AFP, β-HCG, Inhibin A, Inhibin B and CA-125.

A full evaluation of the history and physical examination, imaging studies and tumor markers can allow for reliable preoperative risk stratification and appropriate patient selection for OSS. Papic *et al.* [16] reported a posttest probability of malignancy of 0.25% if a tumor is less than 10 cm in size, tumor markers are negative and there are no solid components on imaging. Furthermore, several recent reports suggest the need for prospective research efforts to determine the accuracy of preoperative risk stratification of ovarian neoplasms [1,19]. On the basis of available evidence, a multidisciplinary preoperative risk stratification algorithm has been developed and is currently undergoing multiinstitutional prospective investigation across children's hospitals participating in the Midwest Pediatric Surgery Consortium (www.mwspc.org).

RISKS OF ADOPTING OVARY-SPARING SURGERY: RECURRENCE AND TUMOR UPSTAGING

Concerns that OSS will increase recurrence rates and tumor upstaging have prevented broader acceptance of OSS as the initial management for benign

ovarian lesions in children. In terms of tumor recurrence, several studies have demonstrated that OSS results in acceptable rates of recurrence for both benign and malignant lesions. In a recently published single-institutional review of 14 patients with mucinous cystadenomas, 12 were managed with OSS [20]. After a median follow-up of 225 days, there were no recurrences. In another recent review, Abbas *et al.* [21] published their experience of 109 benign ovarian lesions managed with OSS. Of 55 patients with repeat imaging at a median time of 7.6 months postoperatively, the recurrence rate was 10%. Five percentage of patients had repeat surgery for mass enlargement or persistent abdominal pain at a median time of 10.5 months. The authors concluded that these recurrence and repeat surgery rates are clinically acceptable and that OSS should be considered for all pediatric patients with benign ovarian tumors.

The effects of tumor rupture and intraoperative spillage on recurrence rates during OSS have also been investigated. In a review of 53 patients with 59 ovarian neoplasms and a 10% recurrence rate, intraoperative spillage, whether accidental or intentional, was not associated with recurrence [22]. A retrospective review by Childress *et al.* [23] looked at 144 patients who underwent OSS for a mature cystic teratoma. They found that 51% of patients had spillage of cystic fluid during the case, which occurred more commonly in operations completed laparoscopically (63.2 vs. 15.8%, $P < .001$). However, patients who had cyst spillage, regardless of operative approach, did not have a higher likelihood of reoperation for a recurrent lesion ($P = .39$). Also, in the previously mentioned review by Abbas *et al.* [21], neither tumor spillage nor incomplete resection was associated with recurrence in multivariable analyses. Upstaging of a misdiagnosed malignant tumor is the other major potential risk of OSS. Some reports suggest an increased risk of upstaging tumors with intraoperative tumor rupture; however, these studies largely reflect adult patients with epithelial ovarian malignancies, which are extremely rare in children [24,25].

Emphasizing the importance of attempting OSS when appropriate is also relevant because patients with benign ovarian neoplasms have a 10–23% reported risk for developing a second neoplasm (benign or malignant) in the contralateral ovary [26,27]. This may result in accidental castration because of potential contralateral ovarian torsion, or surgical castration if oophorectomy on the remaining ovary is ultimately required for malignant disease. Taken together, these data support OSS as the primary treatment for ovarian lesions that preoperatively have been identified as having a high likelihood of being benign.

CONCLUSION

The management of benign pediatric ovarian neoplasms has evolved over recent years. Disparities in practice patterns by specialty have been identified, which has led to increased multidisciplinary collaboration between pediatric surgeons and gynecologists to promote OSS for lesions with a high likelihood of being benign. One of the remaining challenges is identifying methods to perform accurate preoperative risk stratification of these lesions. Recent studies have identified a constellation of physical examination, imaging and laboratory test results that may help practitioners accurately differentiate between benign and malignant disease before surgery. This information is critical as surgical treatment of malignant disease requires oophorectomy, whereas benign disease allows for OSS in the majority of cases. Prospective studies evaluating the accuracy of preoperative risk stratification models are needed to further promote appropriate adoption of OSS as the standard of care for children with ovarian neoplasms.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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