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Imaging of Adnexal Masses

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Abstract: We review and emphasize the importance of gynecologic ultrasound scan for the preoperative evaluation of adnexal masses. Transvaginal ultrasound performed by a trained clinician has a good sensitivity and specificity for discriminating benign and malignant adnexal masses. In conjunction with a carefully obtained history, assessment of risk factors, a focused physical examination and serum markers, the information obtained by a gynecologic ultrasound evaluation can assist the clinician in the diagnosis and treatment of adnexal masses.
Key words: adnexal masses, gynecological ultrasound, transvaginal ultrasound, Doppler imaging, CA 125, ovarian cancer

Introduction

Adnexal masses are a common gynecologic problem frequently requiring surgical management. Conditions that may present as adnexal masses include lesions of the ovary (eg, functional cysts, endometriomas, teratomas, benign, borderline and malignant ovarian tumors), fallopian tube (eg, hydrosalpinx, ectopic pregnancy, tubo-ovarian abscesses), uterus (eg, pedunculated leiomyomas) and less commonly nongynecologic causes (eg, peritoneal cysts, appendiceal and diverticular abscesses, gastrointestinal and metastatic tumors). Of these, ovarian masses are common with up to 10% of women undergoing some form of surgery during their lifetime for the presence of an ovarian lesion.[1] Age, menopausal status, and family history of breast or ovarian cancer are important risk factors for the incidence of malignancy in ovarian tumors.[2] Accurate characterization of adnexal masses poses a challenge for clinicians. The principal goal of the evaluation is to (i) identify patients where the adnexal mass likely represents malignancy and hence, refer them to gynecology oncology consultation, (ii) identify patients with benign lesions who may be

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treated by a general gynecologist using a minimally invasive approach, (iii) accurately diagnose conditions requiring acute management (ectopic pregnancy, adnexal torsion, tubo-ovarian abscess), and (iv) yet avoid unnecessary anxiety and unindicated procedures in patients where the mass is likely benign and may resolve over time or, (v) may be managed expectantly, performing a regular ultrasonography follow-up.

The presurgical diagnostic modalities available to the clinician in diagnosing symptomatic and/or incidentally diagnosed adnexal masses include:

(1) history and physical examination;
(2) laboratory testing including tumor markers;
(3) imaging including transvaginal and transabdominal ultrasonography, magnetic resonance imaging, computerized tomography scan, and positron emission tomography.

The purpose of this chapter is to briefly discuss the various modalities available to the clinician in the evaluation of an adnexal mass and emphasize the role of transvaginal ultrasound in this work up to make appropriate diagnosis in clinical practice.

History and Physical Examination

A careful history and physical examination is the first step in the evaluation of a patient presenting with a symptomatic or incidentally diagnosed adnexal mass. In reproductive age women, the initial evaluation of an adnexal mass should begin with a pregnancy test. Once a pregnancy is ruled out, an assessment of the patient's age, menopausal status and symptoms should be performed. Increasing age and postmenopausal status increase the risk of malignancy. Although studies have shown that recent onset of symptoms such as bloating, pelvic or abdominal pain, early satiety and increased abdominal size that is of <12 months' duration and occurs >12 times per month may be suggestive of ovarian cancer, a symptom-based method alone has not been shown to be clinically applicable for screening or evaluation of pelvic masses.[3] Similarly, a family history of cancer, especially of the breast or the ovary, should prompt a thorough evaluation for ovarian cancer.[2] Physical examination may add important information. Palpable ascites or lymph nodes are ominous signs of malignancy. However, pelvic examination has low sensitivity (45%) for detecting an adnexal mass and most clinicians underestimate the size of the mass.[4] Presence of obesity increases the inaccuracy of the pelvic examination. Therefore, to clarify the nature of an adnexal mass, various serum biomarkers are being developed.

Laboratory Testing Including Tumor Markers

The most commonly studied serum marker to assess the likelihood of malignancy in an adnexal mass is cancer antigen 125 (CA 125). This protein is elevated in association with epithelial ovarian malignancies and is Food and Drug Administration approved as a useful tool in detecting residual or recurrent epithelial ovarian carcinoma in patients who have undergone first-line therapy and in monitoring response to therapy for patients with epithelial ovarian cancer. However, it is raised in numerous other conditions including fibroids, endometriosis, adenomyosis, pelvic infection and nongynecologic cancers. Therefore, a raised serum CA 125 is unreliable in differentiating benign from malignant ovarian masses. This is especially true in premenopausal women because of the increased rate of false positives and reduced specificity. Current guidelines do not give any evidence-based threshold for CA 125 in premenopausal women but

recommend that it should be used in the context of other clinical findings.[2] Measurement of CA 125 is more useful in postmenopausal women with an adnexal mass and a value >35 U/mL is considered abnormal and warrants immediate referral to a gynecologic oncology service.[2] CA 125 is primarily a marker for epithelial ovarian carcinoma and is only raised in 50% of early stage disease. Hence it has poor utility as an effective screening modality for adnexal masses. Presently, the only indication for using CA 125 as a screening tool is in women with a family history of hereditary ovarian cancer who have not elected risk-reducing salpingo-oophorectomy where transvaginal ultrasonography and/or CA 125 may be considered at the clinician discretion.[5]

Another biomarker, human epididymis protein 4 (HE4) has recently been identified but has not been approved as a screening test for ovarian cancer in asymptomatic women.[6] Similarly, panels of biomarkers such as OVA1 and risk of Ovarian Malignancy Algorithm (ROMA) have been studied to distinguish between benign and malignant adnexal masses.[2] The OVA1 and OVA1 next generation are qualitative serum tests of 5 analytes [OVA1: CA 125, transthyretin (prealbumin), apolipoprotein A1, β2 microglobulin, and transferrin; and OVA1 next generation: CA 125, follicle stimulating hormone, apolipoprotein A1, β2 microglobulin, and transferrin]. These tests are approved for use in women over age 18 with an ovarian adnexal mass for which surgery is planned, to assess the likelihood that malignancy is present when the physician's independent clinical and radiologic evaluation does not indicate malignancy.[7] The ROMA test takes into consideration the concentration of the CA 125 and HE4 and the patient's menopausal status to generate a score on a scale of 0 to 10, which translates to a high or low likelihood of finding a malignancy based on established cutoffs.[8] Women with ROMA scores above the cutoff have an increased risk of ovarian cancer, and should be referred to a gynecologic oncologist before surgery.[2] On the basis of the currently available tests, clinical history, physical examination, and biomarkers provide limited information regarding the nature (benign or malignant) of the adnexal mass.[2] Therefore, to triage women with adnexal mass to appropriate management, further evaluation of the mass by imaging is indicated.

Imaging

High frequency (5 to 12 MHz) gray scale transvaginal ultrasonography and color Doppler imaging is the mainstay of diagnosis and characterization of adnexal masses.[9] This modality is well tolerated by patients, most cost-effective and widely available to clinicians. Professional societies have developed competency-based curriculums for the education and training of clinicians who perform diagnostic gynecologic ultrasound scans.[10,11] High interobserver agreement has been reported when imaging is performed by expert examiners, making this technique reliable.[12] In a clinical setting; however, experienced ultrasound examiners are not always available; therefore, more objective methods should be available to allow less-experienced ultrasound operators to correctly evaluate adnexal lesions. The International Ovarian Tumor Analysis (IOTA) group, a group that has extensively studied various aspects of gynecologic ultrasonography and biomarkers, has suggested standardized terms, definitions and measurements to describe sonographic features of adnexal tumors to facilitate correct interpretation of results.[13] Figure 1 provides a systematic approach for evaluation of morphologic characteristics of a suspected adnexal mass by gray scale transvaginal ultrasound. Transabdominal sonography

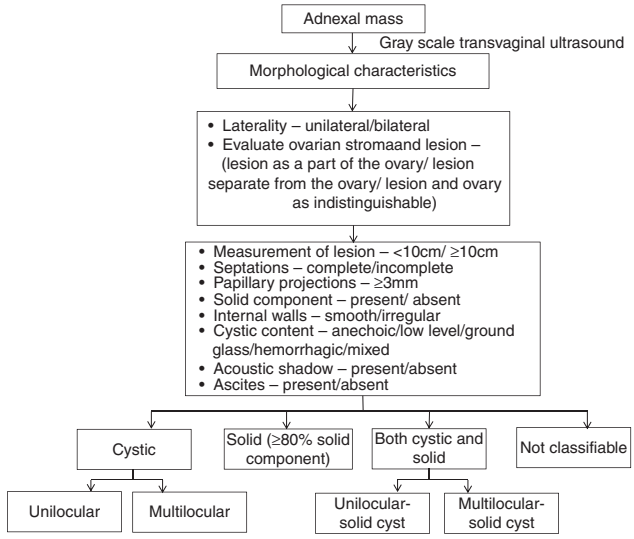


FIGURE 1. Systematic approach for evaluation of morphologic characteristics of a suspected adnexal mass by gray scale transvaginal ultrasound.

should be used to examine a large mass that is not visualized in its entirety using the transvaginal probe. When multiple separate abnormalities are identified, the clinician should systematically document each abnormality. On the basis of this approach, adnexal masses can be qualitatively classified into cystic lesions (unilocular and multilocular cyst), solid lesions, solid-cystic lesions (unilocular-solid cyst and multilocular-solid cyst) and not classifiable.[13]

Following gray scale imaging, the entire tumor should be examined by color Doppler imaging. A subjective semiquantitative evaluation of blood flow in septa, cyst walls, and solid areas of the mass is given, using color/power Doppler[13] (Fig. 2).

SUBJECTIVE ASSESSMENT

Expert ultrasound examiners who spend a majority of their time undertaking gynecologic ultrasound can classify adnexal masses by a subjective impression of the ultrasound morphology and recognizing patterns of findings.[12] On the basis of this subjective assessment, IOTA has proposed classification of adnexal masses into 6 diagnostic categories (ie, certainly malignant, probably malignant, uncertain but more likely malignant, uncertain but more likely to be benign, probably benign or certainly benign). The subjective assessment by an expert ultrasound operator has been recognized

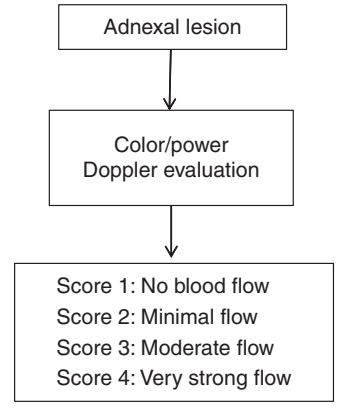


FIGURE 2. Color Doppler evaluation of adnexal masses.

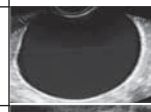
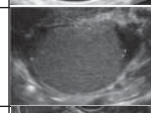
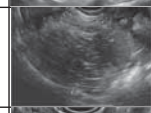
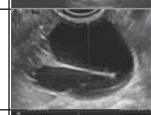
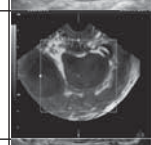
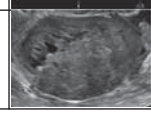
Benign lesion	Image	Ultrasonographic appearance
Simple cyst		Unilocular cyst, regular walls, largest diameter <10 cm in size.
Endometrioma		Unilocular cyst, ground glass echogenicity (homogenous hypoechoic low-level echoes), premenopausal woman.
Dermoid		Unilocular cyst, mixed echoes, acoustic shadows, premenopausal woman.
Hydrosalpinx		Tubular or ovoid anechoic cyst with characteristic incomplete septations or folds. The ovary can be demonstrated out of the cystic lesion.
Tubo-ovarian abscess		Unilocular cystic mass or total breakdown of the normal architecture of one or both adnexa, with formation of conglomerate mass or fluid collection. Probe tenderness, usually acutely ill patient.
Fibroma		Hypoechoic solid concentric lesion with multiple-edge shadows and posterior acoustic attenuation.

FIGURE 3. Ultrasonographic features of common benign adnexal masses.

to be the best performing strategy to characterize adnexal lesions, with a sensitivity of 93% and specificity of 89% of malignancy.[14] Presence or absence of solid components and irregularity has been considered as important predictors of the nature of the adnexal mass.[15]

Some easily recognizable ultrasound characteristics of benign adnexal masses are: thin, smooth wall, absence of papillary projections, septations, solid components and no blood flow on color Doppler imaging. Some benign adnexal masses commonly encountered by clinicians, can be instantly diagnosed by using IOTA Easy Descriptors.[16] The ultrasonographic features of some common benign adnexal masses are summarized in Figure 3.

Similarly, the common ultrasound findings suggestive of malignancy include: size >10 cm, presence of papillary components, septations, irregular walls, solid component, ascites, and high color internal Doppler flow.[2] Late-stage cancers are usually easily identified.

Some adnexal masses may prove to be more challenging to classify as benign or malignant based on ultrasonographic features.[9] The best strategy for classification of these inconclusive results or difficult tumors is subjective assessment of ultrasound images by an expert examiner.[14,17,18] The majority of these unclassifiable tumors after expert subjective evaluation are benign.[9]

Ultrasound-based Scoring Systems and Mathematical Models

To predict malignancy in an adnexal mass, various research-based scoring systems and models have been developed.

Some of these systems (ie, IOTA simple rules) utilize only ultrasound parameters,[18,19] others like Risk of Malignancy Index (RMI) and Assessment of Different NEoplasias in the adneXa (ADNEX) model use a multimodal approach combining information obtained from ultrasound scan with serum CA 125 levels, age, and menopausal status.[20]

SIMPLE RULES

In 2008, the IOTA group described simple rules based on 10 ultrasound features to classify adnexal masses as benign or malignant.[18] Five features (M1, irregular solid tumor; M2, presence of ascites; M3, at least 4 papillary structures; M4, irregular multilocular solid tumors with largest diameter ≥ 100 mm; M5, very strong blood flow) (color score 4) were indicative of malignant tumor (M-features) and 5 features (B1, unilocular tumor; B2, presence of solid component where the largest solid component has a largest diameter < 7 mm; B3, presence of acoustic shadows; B4, smooth multilocular tumor with largest diameter < 100 mm, B5, no blood flow) (color score 1) were indicative of benign tumor (B-features). On the basis of Simple Rules, an adnexal mass is classified as malignant if at least 1 M-feature and no B-feature is present. Similarly, a mass is classified as benign if at least 1 B-feature and no M-feature is present. An adnexal mass cannot be classified if no feature applies or if both M and B features are present. Simple Rules were conclusive in about 75% of adnexal masses and when conclusive they performed as well as subjective assessment by experienced examined for discrimination between benign and malignant masses (sensitivity was 92% and specificity was 96%).[17] The limitations include the inability to estimate the risk of malignancy and the presence of inconclusive results, where the mass cannot be classified as benign or malignant. When all inconclusive results using simple rules would have been classified as malignant, there was a decrease in specificity.[14] In such a situation, subjective assessment of ultrasonographic findings by an experienced examiner was the most accurate approach.[17] Use of the Simple Rules as a triage test and subjective assessment for those masses for which the simple rules yielded an inconclusive result gave a sensitivity of 91% [95% confidence interval (CI), 88%-93%) and a specificity of 93% (95% CI, 91%-94%).[17] To overcome the above limitations a risk model based on the Simple Rules was recently proposed.[21] This new classification system is able to assign a risk of malignancy to all adnexal masses with a good diagnostic performance both in oncology centers where the area under the receiver operating characteristic curve was 0.917 (95% CI, 0.901-0.931) and other centers.[21] In 2011 the Royal College of Obstetricians and Gynaecologists included the IOTA Simple Rules in their Green Top Guidelines for the management of suspected ovarian masses in premenopausal women.[21]

LOGISTIC REGRESSION MODEL

The IOTA logistic regression model LR2 incorporates 6 variables[1] patient age (y), presence of ascites (yes/no), presence of blood flow within a papillary projection (yes/no), maximum diameter of the solid component (mm), irregular internal cyst walls (yes/no) and presence of acoustic shadows (yes/no).[19] A 2-step strategy with simple rules with LR2 used in inconclusive tumors can be a valid alternative if an expert is not available.[14]

Multimodal Tests

RMI

RMI first described in 1990 is a multimodal test incorporating ultrasound findings, menopausal status and serum CA 125 level.[20] Five ultrasound features suggestive of cancer

incorporated in the ultrasound score (U) include: multilocularity, solid areas, bilateral masses, ascites and evidence of metastases. Depending on the findings, U is assigned a value of 0 when none of these features are present, 1 if 1 feature is present, and 3 if 2 or more features are present. A score (M) of 1 is assigned to premenopausal women and 3 to postmenopausal women. RMI is defined as U × M × [serum CA 125 (U/mL)]. An RMI of $\geq$200 is considered an indication of cancer. Currently, the United Kingdom's National Institute for Health and Clinical Excellence (NICE) guidelines for early detection and treatment of ovarian cancer recommend the calculation of RMI version I as part of the evaluation.[22] However, several systematic reviews comparing the accuracy of subjective assessment, simple rules, LR2 and RMI, showed that Simple Rules [sensitivity 0.93 (95% CI, 0.91-0.95) and specificity 0.80 (95% CI, 0.77-0.82)] and LR2 [sensitivity 0.93 (95% CI, 0.89-0.95) and specificity 0.84 (95% CI, 0.78-0.89)] outperformed RMI [sensitivity 0.75 (95% CI, 0.72-0.79) and specificity 0.92 (95% CI, 0.88-0.94)].[14]

ADNEX Model

To develop a risk prediction model to preoperatively discriminate between benign, borderline, stage I invasive, stage II-IV invasive and secondary metastatic ovarian tumors, the IOTA group introduced the ADNEX model.[23] This model contains 3 clinical [age, serum CA-125 level, type of center (oncology centers vs. other hospitals)], and 6 ultrasound predictors [maximum diameter of lesion (mm), proportion of solid tissue (%), >10 cyst locules (yes/no), number of papillary projections (0,1,2,3, > 3), acoustic shadows (yes/no), and ascites (yes/no)]. In a multicenter prospective cohort study, the ADNEX model discriminated well between benign and malignant tumors and offered a fair to excellent discrimination between the 4 types of malignancy.[23]

Clinicians who do not perform diagnostic gynecological ultrasound scans themselves, should establish referral services with providers who routinely perform these ultrasound scans and develop a system to promptly obtain results.

Other Imaging Modalities

The role of other imaging modalities in characterization of adnexal masses such as conventional and contrast enhanced magnetic resonance imaging, computerized tomography and ^{18}F—flurodeoxyglucose positron emission tomography is increasingly being studied.[9]

Conclusions

We have attempted to give an overview of the preoperative evaluation of adnexal masses and discussed the importance of a systematic examination of the pelvic organs, by ultrasound both transvaginally and transabdominally. It is worth emphasizing that clinicians who perform diagnostic gynecologic ultrasound scans should continuously update their knowledge about recent advances in both imaging technology and newer prediction models. Performing gynecological ultrasound on a regular basis and regularly correlating the presumed diagnosis with histopathologic analysis reports can improve diagnostic accuracy.

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