Adnexal Mass

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Presenter Disclosure

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Learning Objectives

• Be able to differentiate adnexal masses
• Determine which are benign and which are malignant
• Understand which testing modality to use
• Be able to determine best treatment approach
• Uterine adnexa consist of ovaries, fallopian tubes, and its surrounding vascular, lymphatic and connective tissues

• Estimated that between 5-10% of women in their lifetime will undergo surgery for potential ovarian neoplasm

• Prevalence of adnexal lesions in clinically asymptomatic women has been approximately 2.5% to 8%
Clinical Approach

• Determine the etiology of the adnexal mass
• Must make sure that the condition is not emergent or poises to cause serious health issues
• Decision should be guided by
  • Age of patient
  • Reproductive status
  • Location of mass
Anatomic Location

- **Ovary**
  - Physiologic cyst
  - Benign ovarian neoplasm
  - Ovarian cancer or metastatic

- **Fallopian tube**
  - Tuboovarian abscess
  - Ectopic pregnancy
  - Hydrosalpinx
  - Fallopian tube cancer

- **Connective & surrounding tissues**
  - Paratubal or paraovarian cyst
  - Broad ligament leiomyoma
Differential Diagnosis

- Gynecologic
- Non-Gynecologic
Differential Diagnosis

• **Gynecologic**
  • **Benign**
    • Functional cyst, endometrioma, mature cystic teratoma, theca lutein cyst, luteoma of pregnancy, corpus luteal cyst, hydrosalpinx, ectopic, leiomyoma, tubo-ovarian abscess, paratubal cyst
  • **Malignant**
    • Epithelial ovarian cancer, borderline tumors, germ cell tumor, sex-stromal tumor, metastatic
    • Most common metastatic disease would be from breast or GI
Differential Diagnosis

• Non-Gynecologic
  • Benign
    • Appendiceal abscess, diverticular abscess, bladder/ureteral diverticulum, pelvic kidney, peritoneal cyst, ovarian remnant
  • Malignant
    • Appendiceal tumor, bowel tumor, metastatic (breast, lung, lymphoma), retroperitoneal sarcoma
Age Group Stratification

- Fetuses
- Children
- Adolescents
- Premenopausal
- Menopausal
Age Group Stratification

• Fetuses
  • Increase in frequency with gestational age
  • Increase in patients with underlying diabetes mellitus, preeclampsia, rhesus isoimmunization

• Newborn
  • Most likely physiological that is due to circulating maternal hormones in utero

• Differentials
  • Genitourinary: reproductive tract anomalies, urinary tract obstruction, urachal cyst
  • Gastrointestinal: mesenteric/omental cyst, volvulus, colonic atresia, intestinal duplication,
  • Others: Choledochal, splenic, or pancreatic cyst, lymphangioma
• Children
  • Physiologic cyst are uncommon due to decrease in gonadotropin ovarian stimulating hormones
  • If present, most simple cysts are due to enlarging cystic follicle

• Adolescent
  • Develops complex and simple cyst
  • Most simple cysts are due to failure of maturing follicle to ovulate and involute
  • Ovarian neoplasms (benign & malignant) accounts for 1% of all tumors in children and adolescent
  • Less than 5% of ovarian cancer occurs in this age group
• In women <25 years old, ovarian malignancy would be the most common gynecologic malignancy

• Germ cell tumors would be the most common, comprising of approximately one-half to two-thirds of ovarian neoplasm up to 18 years old as compared to adult women which would be approximately one-fifth

• In girls <9 years old, approximately 80% of ovarian neoplasms are malignant

• Epithelial ovarian cancers are rare in the prepubertal age group
• Premenopausal women
  • Adnexal masses are stimulated by hormones specific in this age group
  • Ovarian or tubal malignancies are uncommon, however, germ cell tumors would be the most common with peak age between 10 and 30
• Functional/corpus luteal cyst
  • Arise when rupture does not occur and the follicle continues to grow
  • Can become hemorrhagic
  • Typically resolves on its own
  • Can cause complications associated with torsion, hemorrhage, or pain

• Polycystic ovaries
  • Enlarged ovaries with multiple small follicular cysts
  • Rotterdam criteria

• Theca lutein cysts
  • Luteinized follicle cysts as a result of hyperstimulation from elevated hCG or increase sensitivity
  • Bilateral, multiseptated in women with GTD, multiple gestation, ovarian hyperstimulation or pregnancy complicated by fetal hydrops
  • Most are asymptomatic, but can cause maternal virilization, hyperemesis gravidarum, preeclampsia, or thyroid dysfunction
• Ectopic Pregnancy
  • Seen as an adnexal mass on ultrasound

• Corpus Luteum of pregnancy
  • Associated with early intrauterine pregnancy

• Luteoma
  • Non-neoplastic ovarian mass associated with pregnancy
  • Solid component
  • Resolves spontaneously after delivery
  • Should be suspected in the presence of solid adnexal mass, maternal hirsutism or virilization
Premenopausal

- Stimulated by reproductive hormones
  - Endometrioma
    - Related with endometriosis
    - First described by Karl Freiherr Von Rokitansky 1860
    - Original theories: Meyer, Novak, Halban, Sampson
    - Histopathology with endometrial glands and stroma along with hemosiderin macrophages
    - Ultrasound: “ground glass” internal echos
  - Leiomyoma
    - Benign neoplasm of smooth muscle origin
    - Usually arises from uterus
    - Can arise from broad ligament
• Infectious/Inflammatory
  • Tubo-ovarian abscess
    • Results from upper genital tract infection
    • Fever
    • Abdomino-pelvic pain
    • Purulent cervical discharge
    • Palpable mass
    • Cervical motion tenderness

• Hydrosalpinx/pyosalpinx
  • Untreated or undertreated of PID resulting in scarring
  • Collection of tubal secretion or pus
  • Contribute to infertility
Premenopausal

• Benign neoplasm
  • Serous or mucinous cystadenoma
    • Most common benign ovarian neoplasm
    • Thin-walled
    • Uni or multilocular
    • Ranges from 5 to 20cm
  • Mucinous
    • Less common
    • Multiloculated
    • Large size
    • 5% bilateral
    • Collects mucin in their cytoplasm
    • Resembles endocervical or GI epithelium
  • Serous
    • More common
    • 20 to 25% bilateral
    • Similar to fallopian tube lining
• Benign neoplasm
  • Mature cystic teratoma
    • Common in 2nd to 3rd decade of life
    • Cell layers from ectoderm, endoderm, mesoderm
    • US: complex mass, hyperechoic contents, fluid, areas of acoustic shadowing
    • Bilateral in 10 to 15% of patients
  • Endosalpingiosis
    • Non-neoplastic ectopic cystic glands outside of the fallopian tube that are lined with fallopian type ciliated epithelium
  • Paraovarian/paratubal cyst
    • Originate from remnants of paramesonephric or mesonephric ducts
    • Hydatid cyst of morgagni are most common
    • No data to suggest these cyst are malignant or its prevalence
    • Key to diagnosis is noted a simple cyst located next to the ovary on ultrasound
Premenopausal

• Malignant adnexal mass
  • Incidence ranges from 6 to 11%
  • Mostly derived from epithelial cells, but can arise from germ cell, sex-stromal and mixed
  • Can be non-gynecologic metastatic cancer
    • Krukenberg tumor
Menopausal

- Most adnexal cyst are benign
- However, up to 30% can be malignant in patients over the age of 50
  - Malignancy can be gynecologic origin such as endometrium or metastatic from breast or GI
- Can have similar etiologies of adnexal cyst for premenopausal women
- Simple cysts are common and are from persistent physiologic/functional cyst
- Characteristic for benign versus malignant is similar to those of premenopausal, however one must have a lower threshold for suspicion
• Neoplasms
  • Includes Epithelial (75%), Sex-stromal (15%), and Germ cell (10%)
  • Epithelial carcinoma is most common histological type in this age group and encompasses approximately 90% of ovarian, peritoneal, and tubal carcinoma
  • It has been proposed that origin of high grade serous tumors may originate from fallopian tube precursors
  • Average age is approximately 60 years old
  • Include vague GI symptoms: dyspepsia, early satiety, anorexia, constipation, and bloating
Menopausal

- Epithelial
  - High grade serous carcinoma (70-80%)
  - Endometrioid (10%)
  - Clear cell (10%)
  - Mucinous (3%)
  - Low grade serous carcinoma (5%)

- Sex-stromal: often produces estrogen/androgen
  - Granulosa cell
  - Fibroma
  - Thecoma
  - Sertoli-Leydig

- Germ cell
  - Dysgerminoma
  - Endodermal sinus tumor
  - Immature teratoma
  - Gonadoblastoma
  - Choriocarcinoma
  - Seminoma
  - Embryonal carcinoma
• Regardless of age group, can always be malignant
• Might be signs of metastatic disease
• Must rule out ectopic pregnancy as it can affect fertility and be life-threatening
• Can rupture
• Causes torsion which can result in diminishing blood supply to the ovary
• Hemorrhagic cyst can cause bleeding
• Do I need to remove it?
• Am I dealing with potential cancer?
• Is the patient stable?
• Are there conservative alternatives?
• What tests do I have to order that will assist me in making my decision?
• Do I need a referral?
• Need diagnostic tests which has higher sensitivity and specificity that will enable us to make better decisions

• What will guide most of us?
  • History
  • Physical
  • Imaging
  • Laboratory tests

• Most common imaging a gynecologist will use is an ultrasound

• Most common laboratory test order to differentiate variety of benign conditions versus malignant ones are tumor markers
• Goal of an ultrasound is not to determine 100% whether or not a mass is benign or malignant
• The purpose of the ultrasound is to guide our decision making
• Fortunately, ultrasound is a highly effective, cheap, and safe tool to use
• adsfs
Ultrasound

• Sonogram techniques
  • Gray scale
    • Based on signal intensity and depth measured it length of time it require for wave to be reflected back
  • Doppler
    • Change in frequency that results from sound wave being reflected off moving objects, i.e. blood vessel
  • Combined gray scale & doppler
    • Prefered method
• 3-D techniques
  • Does not improve detection between benign and malignant process
  • May assist with detection of hydrosalpinx
• Spectral doppler
  • Too broad of overlap in resistive index and pulsatility index between benign and malignant masses
  • Velocity and diastolic notch measurements does not appear to improve reliability
• Consulsion: stay simple, go with gray scale and color doppler
Steps in characterizing a mass

- Is it a simple cyst?
  - Anechoic fluid filled cavity
  - Thin walls
  - No impaired sound wave

- Are there other physiological process that can be a cause if the cyst does not appear simple?
  - Corpus luteum
    - Thickened wall
    - Circumferential color doppler flow
    - Small central lucency that could be confusing
  - Multiple simple cyst
    - Misdiagnosed as having septation
  - Hemorrhagic cyst
    - Can have septation and mural nodules
    - Usually have thin linear echos (fishnet or reticular pattern)
    - Linear echos do not extend completely uninterrupted
Ultrasound

Are there characteristics that are specific to other “entities”?

- **Endometrioma**
  - Homogeneous low to medium echos
  - Can have solid components and be either unilocular or multilocular
  - Can have doppler flow especially if foci of endometrial tissue
  - Have similar findings of hemorrhagic cyst

- **Mature teratoma**
  - Markedly hyperechoic nodule within the mass
  - Contain fluid, Calcification with usually no color flow

- **Pedunculated leiomyoma**
  - Heterogeneous, hypoechoic, solid masses

- **Hydrosalpinx**
  - Tubular structure with septation or nodules in the wall

- **Peritoneal inclusion cyst**
  - Can have septated features around the ovary in women with adhesions
  - Adhesions can be seen as bands of tissue with surrounding fluid

- **Malignancy**
  - Solid component, not hyperechoic, has nodularity or papillary
  - Septations thicker than 2-3mm
  - Color doppler flow in the solid component
  - Presences of ascites
  - Peritoneal masses, enlarged nodes or matted bowels
  - Size of the mass does not clearly define malignancy
International Ovarian Tumor Analysis (IOTA)

- Largest diagnostic accuracy study
- Ultrasound performance determine on the level of “risk of malignancy”
- 4848 patients from oncology and non-oncology centers
- Diagnostic criteria based on “Simple rules”
- 23% had low risk (<1%)
  - Sensitivity 99.7%, specificity 33.7%,
  - PPV 44.8%, NPV 98.9%
- 48% had high risk (>30%)
  - Sensitivity 89%, specificity 84.7%
  - PPV 75.4%, NPV 93.9%
Ultrasound

- From IOTA study
- Simple rules
  - Benign features
    - Unilocular cyst of any size
    - Solid components either not present or <7mm
    - Presence of acoustic shadowing
    - Smooth multilocular cyst <10cm
    - No blood flow
  - Malignant features
    - Irregular solid tumor
    - Ascites
    - At least four papillary structures
    - Irregular solid-multilocular tumor, largest >10cm
    - Very strong color doppler flow
• If still inconclusive, what other options are available?
  • Repeat ultrasound
    • Only if there is suspicion that process could be physiological process
    • Try to obtain ultrasound in follicular phase, around day 7-12 to reduce risk of hemorrhagic cyst in the next cycle
    • Difficulties due to irregular cycle
  • MRI
    • Can be good modality if surgical treatment is to be considered
    • Irrelevant for determining benign versus malignant adnexal mass if surgical intervention would be carried out by a gynecologic surgeon experience in dealing with malignancy
  • Rely on laboratory results
  • Referral to gynecology oncologist
Serum Markers

• Biomarker: a characteristic that is objectively measured and evaluated as an indicator of normal processes, pathological processes, or response to intervention

• Tumor marker: specific biomarker for malignancy

• When dealing with adnexal masses and concern for malignancies, Epithelial ovarian cancer (EOC) is the most common and most concerning

• There are no markers developed for the purpose of evaluating benign processes, though certain benign processes can cause elevation in tumor markers more specific for malignancies

• There are numerous markers for different types of adnexal malignancies, most common, ovarian.

• CA125, CA19-9, CEA, Inhibin, AFP, betaHCG, LDH, etc.
Serum Markers

• Evaluate most commonly used marker: CA125
  • First described in 1983
  • Large transmembrane glycoprotein derived from both coelomic and mullerian epithelia
    • Coelomic: pericardium, pleura, peritoneum
    • Mullerian: Fallopian tube, endometrium, endocervical
  • Approved by FDA to monitor response to therapy in women with known EOC
  • Two types: CA125 and CA125 II, different cut off values
  • No current data available to support superiority of one versus the other
  • CA125 can be elevated in other non-malignant conditions
  • Not overly useful in premenopausal patients unless “significantly” elevated
  • Usually, a cut-off of 200 u/ml for premenopausal patients is used
  • CA125 and CA125 II cut-off for menopausal: 35 u/ml and 20 u/ml
Serum Markers

• Human epididymis protein 4
  • Antigen derived from human epididymis protein, a product of the WFDC2 gene that is overexpressed in patients with serous or endometrioid ovarian carcinoma
  • FDA approved in 2008 for monitoring recurrent or progressive disease in patients with EOC
  • HE4 < 150 pM
  • Used in conjunction with ROMA

• Carcinoembryonic antigen
  • Protein found in embryonic or fetal tissue (disappear after birth)
  • Mucinous cancer of GI tract or ovary
  • Can be elevated in breast, pancreatic, thyroid, lung cancers
  • Benign conditions include: cigarette smoking, mucinous cystadenoma of ovary or appendix, cholecystitis, liver cirrhosis, diverticulitis, IBD, pancreatitis, pulmonary infections
  • Can be used to monitor patients with pseudomyxoma peritonei
Serum Markers

- CA19-9
  - Mucin protein marker
  - Elevated in mucinous ovarian tumors
  - Monitor response to therapy or recurrence in patients with gastric, pancreatic, gallbladder cancer, cholangiocarcinoma, and adenocarcinoma of the ampulla of Vater

- OVA1 (Quest diagnostics)
  - Includes 5 serum markers
  - FDA approved in 2009 to assess likelihood of malignancy in patient undergoing surgery for an adnexal mass
  - CA125 II, Beta 2 macroglobulin, transferrin, transthyretin, apolipoprotein A1
  - Premenopausal
    - Low probability of malignancy: < 5
    - High probability of malignancy: > 5
  - Postmenopausal
    - Low probability of malignancy: < 4.4
    - High probability of malignancy: > 4.4
  - Triglyceride levels exceeding 4.5g/L or rheumatoid factor > 250 IU/ml may interfere
• Risk of malignancy algorithm (ROMA)
  • FDA approved in 2011 to assess women for planned surgery to detect risk of malignancy
  • Uses CA125 and HE4 through an algorithm depending on menopausal status
  • Premenopausal: high risk > 13.1%
  • Postmenopausal: high risk > 27.7%
  • Available internationally on websites and smartphone applications

• Risk of malignancy index (RMI I-IV)
  • Originally developed in 1990
  • Use primarily in UK
  • Combines CA125, pelvic ultrasound (U), and menopausal status (M)
  • RMI I = U x M x CA125, if score is >200, should refer to specialist
  • Ultrasound: multi-locular, solid areas, metastasis, ascites, bilateral masses
  • Size <7cm or >7cm
• ADNEX model
  • Designed for use in women with adnexal mass planning for surgery
  • First reported in 2014
  • Predict not only about malignancy versus benign, but also borderline, stage I-IV, and secondary metastatic adnexal tumors
  • Has not been validated outside of European research collaborative group
  • Computerized model that combines different characteristic
    • Age
    • CA125
    • Type of center
    • Ultrasound features: maximum diameter of lesion, proportion of solid tissue, >10 cyst locules, number of papillary projections, acoustic shadows, ascites

• www.iotagroup.org/adnexmodel/
• Diagnostic performance
  • CA125
    • Alone has low sensitivity and specificity, especially for early stage ovarian cancer with sensitivity of 25% and specificity of 61%
    • Meta-analysis of 77 studies with value >35 U/mL had a sensitivity and specificity of 78%, low values secondary to other types of ovarian malignancy that does not have elevated CA125, i.e. mucinous, clear cell, mix mullerian ovarian tumors
    • Premenopausal: Sensitivity 50-74%, specificity 69-78%, due to benign causes of CA125 elevation
    • Postmenopausal: Sensitivity 69-87%, specificity 81-93%
  • OVA1
    • Prospective series with 524 women, compared OVA1 with CA125 II and clinical assessment
      • OVA1 sensitivity 93% and specificity 43%, CA125 sensitivity 69% and specificity 84%, clinical assessment sensitivity 75% and specificity 79%
      • With menopausal status: Higher sensitivity with OVA1 100% versus CA125 92%
      • Higher sensitivity in OVA1 versus CA125 in Stage I and II primary ovarian cancer
    • Improved diagnostic tool compared to CA125 alone
• Diagnostic Performance
  
  • ROMA
  
  • Prospective multi-institutional study of 531 patients
    • High risk patient (Incidence of malignancy 24%)
    • Post menopausal: Sensitivity 92%
    • Premenopausal: Sensitivity 76%
  
  • Prospective multi-institutional study of 472 patients
    • Low risk patients (Incidence of malignancy 10%)
    • Postmenopausal: Sensitivity 92% and specificity 76%
    • Premenopausal: sensitivity 100% and specificity 74%
  
  • ROMA versus HE4 versus CA125
    • ROMA was most sensitive (86%: 80%: 84%)
    • HE4 was most specific (84%: 94%: 78%)
    • Results however are not statistically significant
• Diagnostic performance
  
  • RMI
    • Similar sensitivity and specificity among RMI I through IV
    • Advantages over serum biomarkers is that it combines most important clinical elements in predicting malignancy
    • Disadvantage is that the risk calculator uses absolute CA125 level instead of a scoring system. Patients with early stage cancer can often have low CA125 and be misleading

  • ADNEX model
    • No validation study available at this time
• Conclusion:
  • Not all adnexal masses are malignant
  • Tumor markers and ultrasounds are to guide us in differentiating between benign and malignant with a certain level of confidence
  • CA125 is NOT used as a cancer screening
  • OVA1 & ROMA are additional tools which are available to aide in deciding benign versus malignant. They should be used in patients that are already undergoing planned surgery
  • When in doubt, ask a colleague
Thank You!